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CHOICE OF SULFONAMIDE DRUGS FOR LOCAL USE

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THE increasing availability of penicillin, and more recently of streptomycin, has led to the less frequent use of the sulfonamide compounds as ocular therapeutic agents. In several instances these antibiotics are superior to the sulfonamide compounds. Penicillin is locally effective in the presence of purulent material. It is very effective against ocular infections due to many gram-positive organisms, and streptomycin is effective against several gram-negative organismal infections.

There are many occasions, however, when the so-called antibiotics will not be helpful. Organisms become resistant to the effects of penicillin, and especially to streptomycin. These agents rapidly lose their potency when not kept under refrigeration, particularly when in solution. Some patients acquire hypersensitivity to penicillin or streptomycin. In any of these predicaments the substitution of one of the sulfonamide drugs might be beneficial.

Although it is not universally accepted,[1] there is evidence that the sulfonamide compounds are effective as bacteriostatic agents when applied locally to the ocular tissues.[2] It has been found that the higher the concentration of the sulfonamide drug obtained in the infected tissue, up to a point, the better have been the results in controlled ex-

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From the Department of Ophthalmology, University of Pennsylvania.

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2. *(a)* Rambo, V. C.: Treatment of Pathological Ocular Conditions with Sulfanilamide, Am. J. Ophth. **21**:739 (July) 1938. *(b)* Johnstone, I. L.: Sulphonamide Treatment of Hypopyon Ulcer of the Cornea, Brit. M. J. **1**:887 (June 14) 1941. *(c)* Robson, J. M., and Scott, G. I.: Effect of Certain Chemotherapeutic Agents on Experimental Eye Lesions Produced by Staphylococcus Aureus, Nature, London **149**:581 (May 23) 1942; *(d)* Local Effectiveness of Sodium Sulphacetamide in Treatment of Experimental Ulcers of the Cornea, Brit. M. J. **1**:5 (Jan. 3) 1942; *(e)* Local Treatment of

(Footnote continued on following page)

perimental infection.[3] Comparisons of the various methods of administration, as well as of the various sulfonamide drugs, have been made in an effort to determine the simplest method of reaching the highest concentration in a particular tissue.[4] The problem of the choice of a particular sulfonamide drug has been complicated with many factors. Each year new sulfonamide compounds have become available. Each compound has had a particular merit extolled. Most of these substances have been tried in the treatment of pneumonia, gastrointestinal infections and in urinary infections. The usefulness of only a few has been tested in the management of ocular infections and their ability to penetrate ocular tissues measured. In an effort to review the many problems encountered in the selection of the proper sulfonamide compound and the acceptable local methods of administration, the following experiments are reported.

METHOD OF STUDY

Normal rabbit eyes were used. The rabbits were chinchillas, weighing approximately 4 Kg. The aqueous humor of these eyes yielded from 0.2 to 0.25 cc. per punc-

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Experimental Pyocyaneus Ulcers of the Cornea with Albucid Soluble, Nature, London **148**:167 (Aug. 9) 1941. *(f)* Scott, G. I., and others: Discussion of the Value of Sulphonamides in Ophthalmology, Tr. Ophth. Soc. U. Kingdom **62**: 3, 1942. *(g)* Dickson, R. M.: Traumatic Ulcer of Cornea with Special Reference to Coal Miners, Brit. J. Ophth. **26**:529 (Dec.) 1942. *(h)* Bellows, J. G.: Chemotherapy in Ophthalmology, Tr. Am. Acad. Ophth. **47**:19 (Sept.) 1942. *(i)* Leopold, I. H., and Scheie, H. G.: Studies with Microcrystalline Sulfathiazole, Arch. Ophth. **29**:811 (May) 1943. *(j)* Thygeson, P.: Sulfonamide Compounds in Treatment of Ocular Infections, ibid. **29**:1000 (June) 1943. *(k)* Thygeson, P., and Braley, A. E.: Local Therapy of Catarrhal Conjunctivitis with Sulfonamide Compounds, ibid. **29**:760 (May) 1943. *(l)* von Sallmann, L.: Sulfadiazine Iontophoresis in Experimental Pyocyaneous Ulcer of Rabbit Cornea, Am. J. Ophth. **25**:1292 (Nov.) 1942. *(m)* Alvaro, M. E.: Clinical Effects of Local Use of Sulfonamides on Eyes, ibid. **28**:497 (May) 1945. *(n)* Vorisek, E. A.: Evaluation of the Newer Therapeutic Agents in Ophthalmology, ibid. **30**:29 (Jan.) 1947.

3. Robson and Scott (footnote 2*c*, *d* and *e*). Scott and others.[2f] von Sallmann.[21]

4. Leopold and Scheie.[21] von Sallman.[21] Guyton, J.: Use of Sulfonamide Compounds in Ophthalmology, Am. J. Ophth. **22**:833 (Aug.) 1939; Local Use of Sulfonamide Compounds in the Eye, ibid. **24**:292 (March) 1941. Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:406 (Sept.) 1939. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, ibid. **27**:34 (Jan.) 1942. Pan, S. Y.: Distribution of Sulfanilamide in the Ocular Fluids and Tissues After Local Application, Proc. Soc. Exper. Biol. & Med. **46**:31 (Jan.) 1941. Gallardo, E., and Thompson, R.: Sulfonamide Content of Aqueous Humor Following Conjunctival Application of Drug Powders, Am. J. Ophth. **25**:1210 (Oct.) 1942. Boyd, J.: Sodium Sulfathiazole Iontophoresis, Arch. Ophth. **28**:205 (Aug.) 1942. Robson, J. M., and Tebrich, W.: Penetration of a Water-Soluble Sulphonamide, Sodium Sulphacetamide into the Eyes of Rabbits, Nature, London **148**:695 (Dec. 6) 1941.

ture. At the desired interval after application of the sulfonamide preparation, the eyes were thoroughly washed with a 1.4 per cent solution of sodium chloride, and 2 drops of 1 per cent tetracaine hydrochloride was instilled for local anesthesia. Punctures were made into the anterior chamber with a tuberculin syringe and a no. 22 hypodermic needle. The method of Bratton and Marshall[5] was used for determining the levels of free sulfonamide. Standard curves for known quantities of each sulfonamide compound were determined. Recoveries on normal aqueous humor showed that an error of less than 3 per cent could be expected with this method. An Evelyn photoelectric colorimeter was used in the procedure.

Sulfonamide compounds in their acid form are not sufficiently soluble in water to be used as solutions in clinical work. Their sodium salts are freely soluble, and therefore solutions of 5, 10 and 20 per cent concentrations were employed in these experiments. Calcium sulfadiazine is soluble up to 5 per cent, and only this concentration was used. Ammonium sulfadiazine was tried in 10 per cent concentration.

RESULTS

Table 1 records the concentration of the sulfonamide compound in the aqueous humor fifteen minutes after application to normal rabbit

TABLE 1.—*Penetration into the Anterior Chamber of Normal Rabbit Eyes of Locally Applied 10 Per Cent Solutions of Sodium Salts of Various Sulfonamide Compounds and 5 Per Cent Calcium Sulfadiazine*

	Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor					
10% Sodium Sulfadiazine	10% Microcrystalline Sulfadiazine	10% Sodium Sulfacetimide	10% Sodium Sulfamezathine	10% Sodium Sulfamerazine	10% Ammonium Sulfadiazine	5% Calcimu Sulfadiazine
0.06	0.11	0.17	1.71	1.6	0.68	0.57
0.23	0.17	0.28	0.68	0.46	0.91	0.34
0.23	0.06	0.23	2.5	0.57	1.30	0.40
0.26	0.57	0.17	1.8	0.23	0.91	0.45
0.28	0.50	0.24	1.6	0.23	...	0.50
0.34	0.23	0.26	...	...	...	...
0.23	...	...	...	...	...	...
0.34	...	...	...	...	...	...

eyes of 4 drops of 10 per cent solutions of sodium sulfadiazine, 10 per cent ammonium sulfadiazine, 5 per cent calcium sulfadiazine, 10 per cent sodium sulfacetimide (sodium salt of para-aminobenzene sulfonylacetylimide; acetylsulfanilamide), 10 per cent sodium sulfamezathine (sodium salt of the dimethyl derivative of sulfadiazine) and 10 per cent sulfamerazine sodium U.S.P. The levels after applying 0.3 Gm. of 15 per cent microcrystalline sulfadiazine are also recorded. Only sodium sulfamezathine penetrated significantly better than the others.

Table 2 presents the results when these agents were applied in an ointment base (samples of aqueuos humor were withdrawn fifteen minutes after application of the ointment). No significant difference could be detected between the various compounds, nor did it matter whether the ointment base was of the oil in water type, such as Fried-

5. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537, 1939.

enwald-Fuqua ointment,[6] or the water in oil type, such as "aquaphor."[7] The aqueous levels obtained with ointment preparations in the normal eye were approximately the same as those with solutions. The acid form also penetrated as well as the sodium salt.

TABLE 2.—*Penetration into the Anterior Chamber of Sulfonamide Compound in Ointment Bases*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor				
10% Sulfadiazine	10% Sodium Sulfadiazine	10% Microcrystalline Sulfadiazine	10% Sodium Sulfacetimide	10% Sulfacetimide
		"AQUAPHOR" BASE		
0.57	0.00	0.23	0.34	0.23
0.00	0.23	0.34	0.68	0.66
0.00	0.00	0.46	0.23	0.23
0.06	0.11	0.44	0.80	0.46
0.00	0.06		0.34	0.34
		FRIEDENWALD-FUQUA BASE		
0.11	0.11	0.23	0.06	0.11
0.23	0.46	0.06	0.46	0.11
0.11	0.46	0.06	0.06	0.23
0.17	0.34	0.17	0.24	0.22

In table 3 are given the results of repeated application of the drops, 4 drops every fifteen minutes for three doses, and withdrawal of the aqueous humor fifteen minutes after instillation of the last drop. The concentrations in the aqueous humor were raised slightly over those with one application of 4 drops, but not to an adequate therapeutic level in any eye.

TABLE 3.—*Penetration into Anterior Chamber of 10 Per Cent Solutions of Sodium Sulfacetimide and Sodium Sulfadiazine Repeatedly Applied**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor	
10% Sodium Sulfadiazine	10% Sodium Sulfacetimide
0.10	0.28
0.57	0.34
0.23	0.10
0.90	0.80
0.88	0.90

*Four drops of the solution was applied every fifteen minutes for three doses; fifteen minutes after the last application (one hour after the first application) the specimens of aqueous were taken.

Table 4 records the levels in the aqueous after application of 20 per cent solutions of sodium sulfadiazine and sodium sulfacetimide. Four drops was applied, and punctures were made fifteen minutes later. No significant increase was noted in the normal eye over the concentration reached after the use of 10 per cent solutions. These results indicated that an adequate level in the aqueous humor cannot be expected from application of solutions in the normal rabbit eye.

6. The Friedenwald-Fuqua ointment base contains benzyl benzoate, 5 per cent; peanut oil, 37 per cent; anhydrous wool fat, 8 per cent; cetyl alcohol, 10 per cent; glycerin monostearate, 10 per cent, and white petrolatum U.S.P., 25 per cent.

7. "Aquaphor" is an ointment base containing 6 per cent of a group of esters of cholesterol (chiefly oxycholesterol) in an aliphatic hydrocarbon (petrolatum) base.

Drops of sodium sulfadiazine and sodium sulfacetimide, 10 per cent each in a 0.1 per cent solution of "duponol" (fatty alcohol sulfates) were applied to the right eyes of a series of normal rabbits, and the same sulfonamide drugs were applied in equal quantity to the control (left) eyes without a wetting agent. The results are recorded in table 5. The same procedure was repeated with these compounds in an ointment base. It is shown in this table that the use of a detergent definitely increases the penetration into the anterior chamber of the sulfonamide compound in ointment or in liquid form. The corneas do

TABLE 4.—*Penetration into the Anterior Chamber of Normal Rabbit Eyes of Locally Applied 20 Per Cent Sodium Sulfadiazine, 20 Per Cent Sodium Sulfacetimide and 20 Per Cent Microcrystalline Sulfadiazine**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor		
20% Sodium Sulfadiazine	20% Microcrystalline Sulfadiazine	20% Sodium Sulfacetimide
0.20	0.65	0.11
0.11	0.17	0.28
0.45	0.29	0.46
0.34	0.11	0.23
0.33	0.17	0.57
...	0.30	...

*Applications in each instance were 4 drops, or 0.3., and specimens were taken by puncture fifteen minutes after the last application.

TABLE 5.—*Influence of Detergent on Penetration of Sulfonamide Preparation into Anterior Chamber of Normal Rabbit Eye**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor			
10% Sulfadiazine in Friedenwald-Fuqua Ointment*	10% Sulfadiazine and "Duponol," 0.1% in Ointment	10% Solution of Sodium Sulfadiazine	10% Solution of Sodium Sulfadiazine and "Duponol," 0.1%
O.D.	O.S.	O.D.	O.S.
0.11	0.44	0.28	1.25
0.23	0.68	0.34	0.91
0.17	1.37	0.23	0.66
10% Sulfacetimide in Friedenwald-Fuqua Ointment	10% Sulfacetimide in Ointment and "Duponol," 0.1%	10% Solution of Sodium Sulfacetimide	10% Solution of Sodium Sulfacetimide and "Duponol," 0.1%
O.D.	**O.S.**	**O.D.**	O.S.
0.11	2.96	0.11	2.62
0.17	0.67	0.17	0.83
0.23	2.01	0.26	0.86

*Four drops was applied and specimens were taken fifteen minutes after the last drop.

not stain after such treatment. The concentrations obtained in the aqueous are still not theoretically adequate, but indicate that the corneal levels are at, or are approaching, the therapeutic level. These results simply confirm those of Bellows and others,[8] who have demonstrated the increased penetration of locally applied sulfonamide compounds with various detergents.

All these studies were repeated using rabbit eyes which were contaminated with a measured quantity (0.4 mg.) of mustard gas (2-chloroethyl sulfide). Such a lesion produces loss of corneal epithelium and a severe, persistent inflammatory reaction of the anterior segment.

8. Leopold and Scheie.[21] Bellows, J., and Gutman, M.: Application of Wetting Agents in Ophthalmology, Arch. Ophth. **30**:352 (Sept.) 1943. Ginsburg, M., and Robson, J. M.: Effect of Detergent on the Penetration of Sodium Sulphacetamide into Ocular Tissues, Brit. J. Ophth. **29**:185 (April) 1945.

It is evident from the analyses presented in tables 6, 7 and 8 that the penetration of each of the sulfonamide drugs is greatly increased in the eyes previously burned with mustard gas. It is also evident that one may expect high penetration values even nine days after the initial burn. Sodium sulfacetimide gives higher aqueous levels than sodium sulfadiazine. The sodium salts of sulfamerazine and sulfamezathine penetrate the burned eye better than sodium sulfadiazine, but not quite as well as sodium sulfacetimide.

From the results shown in tables 9 and 10, it is evident that the acid salt of the sulfonamide compounds, as well as their sodium salts,

TABLE 6.—*Penetration of 10 Per Cent Solution of Sodium Sulfadiazine**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor				
	Eyes Burned with Mustard Gas			
Normal Eyes	24 Hours Previously	48 Hours Previously	96 Hours Previously	9 Days Previously
0.00	31.1	53.8	61.6	40.0
0.20	33.5	46.1	46.4	42.0
0.30	34.2	46.1	46.4	42.0
0.23	...	81.4	55.0	59.2
0.26	...	48.3	...	...
0.33	...	60.7	...	...
0.20	...	79.3	...	..

*Four drops was applied and specimens were taken fifteen minutes after the last drop.

TABLE 7.—*Penetration of 10 Per Cent Solution of Sodium Sulfacetimide**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor				
	Eyes Burned with Mustard Gas			
Normal Eyes	24 Hours Previously	48 Hours Previously	96 Hours Previously	9 Days Previously
0.17	124.8	87.2	100.8	83.2
0.28	72.8	119.2	75.2	74.0
0.24	84.0	103.6	52.0	32.4
0.21	...	52.0	...	...
0.21	...	80.0	...	...
0.18	...	88.0	...	...

*Four drops was applied and specimens were taken fifteen minutes after the last drop.

TABLE 8.—*Penetration of 10 Per Cent Sodium Sulfamezathine and 10 Per Cent Sodium Sulfamerazine in Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Drug per 100 Cc. of Aqueous Humor	
Sodium Sulfamezathine, 10% O.D.	Sodium Sulfamerazine, 10% O.S.
37.6	54.3
37.6	44.5
34.2	58.4
38.4	55.0
40.0	57.5

penetrate much more readily in eyes which have been burned with mustard gas. However, the penetration of the acid salt of each sulfonamide compound was not so great as the sodium salt. Also, the penetration of the sodium salt was much greater in a fifteen minute period from a solution vehicle than it was from an ointment vehicle. It is also evident from table 10 that the type of ointment base was an important factor in penetration of the drug into mustard-burned eyes. Here it may be seen that both sodium sulfadiazine and sodium sulfacetimide penetrated much more rapidly from an ointment base such as the

Friedenwald-Fuqua type, which is similar to an oil in water base, than they did from an ointment base such as "aquaphor," which is a water in oil base.

From the results in table 11, it is evident that the sulfonamide drugs in an ointment base reached a high level in the aqueous after

TABLE 9.—*Penetration of 10 Per Cent Sulfadiazine and 10 Per Cent Sulfacetimide in "Aquaphor" Ointment*

Milligrams of Sulfonamide Drug per 100 Cc. of Aqueous Humor			
10% Sulfadiazine in "Aquaphor" Ointment		10% Sulfacetimide in "Aquaphor" Ointment	
Normal Eyes	Eyes Burned with Mustard Gas 24 Hr. Previously	Normal Eyes	Eyes Burned with Mustard Gas 24 Hr. Previously
0.06	0.67	0.44	0.80
0.11	0.93	0.33	0.91
0.20	1.46	0.60	1.14

TABLE 10.—*Penetration of 10 Per Cent Sodium Sulfadiazine and 10 Per Cent Sodium Sulfacetimide in Various Ointment Bases*

Milligrams of Sulfonamide per 100 Cc. of Aqueous Humor							
10% Sodium Sulfadiazine Ointments				10% Sodium Sulfacetimide Ointments			
Normal Eyes	Eyes Burned with Mustard Gas			Normal Eyes	Eyes Burned with Mustard Gas		
	24 Hr. Previously	48 Hr. Previously	72 Hr. Previously		24 Hr. Previously	48 Hr. Previously	72 Hr. Previously
*F.F.	"Aquaphor"	F.F.	F.F.	F.F.	"Aquaphor"	F.F.	F.F.
0.34	0.80	14.4	12.8	0.68	10.83	73.6	50.6
0.38	0.63	11.2	13.6	0.46	12.77	43.2	61.6
0.17	1.06	19.2	14.4	0.36	6.84	89.6	79.1
							92.0
	F.F.				F.F.		
	9.9				48.0		
	18.7				40.8		
	16.6				53.0		
	Hydrous Wool Fat—Petolatum Base						
	0.92						
	1.2						
	1.4						
	1.2						
	Vanisol†						
	6.8						
	6.8						
	7.1						
	5.9						

*Friedenwald-Fuqua ointment base.
†"Vanisol" consists of sodium stearate, 20 per cent; cetyl alcohol, 5 per cent; glycerin monostearate, 8 per cent, and water, 67 per cent.

TABLE 11.—*Penetration of Sulfonamide Compounds in Friedenwald-Fuqua Ointment Base in Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor			
Ointment in Contact with Cornea			
Sodium Sulfadiazine			
15 Min.	1 Hr.	6 Hr.	24 Hr.
14.4	24.0	2.05	1.20
11.2	20.0	2.17	0.40
19.2	20.0	1.94	0.51
Sodium Sulfacetimide			
73.6	144.0	0.46	0.13
43.2	137.6	0.23	0.67
89.6	104.0	1.10	0.23

*Values are expressed as milligrams of the sulfonamide compound per hundred cubic centimeter of aqueous humor.

being in contact with mustard-burned eyes for one hour, that the drugs passed from the aqueous humor at such a rate that adequate levels were not present after six hours and that only very small quanti-

ties remained at the end of twenty-four hours. It is apparent that sulfadiazine tended to pass out of the anterior chamber less rapidly than sulfacetimide. These findings indicate that an ointment would have to be applied a minimum of four times a day, and preferably oftener, in order to maintain a theoretically adequate concentration in the aqueous humor in such eyes. For similar reasons (table 12), solutions should be applied every two hours.

TABLE 12.—*Persistence of Sodium Sulfadiazine in Aqueous Humor of Mustard-Burned Rabbit Eyes After Application of Four Drops of 10 Per Cent Solution of Sodium Sulfadiazine*

Milligrams of Sulfadiazine per 100 Cc. of Aqueous Humor Interval After Application of Last Drop			
15 Min.	1 Hr.	2 Hr.	4 Hr.
30.1	3.7	1.14	0.80
32.0	3.0	2.05	0.68
30.4	4.2	2.14	0.48
32.8	4.9	1.90	0.36

In table 13 is recorded the penetration of microcrystalline sulfadiazine in ointment into the anterior chamber of eyes burned with mustard gas twenty-four hours previously. It is evident that the levels obtained are not better than the levels demonstrated for the macrocrystals of sulfadiazine in the same ointment (compare with table 9). It is apparent that the addition of "duponol M. E. dry," 0.1 per cent, increased the penetration of the microcrystalline sulfadiazine in eyes burned with mustard gas. However, the values obtained were still not so great as those obtained with the sodium salt.

TABLE 13.—*Influence of Detergent on Penetration of Microcrystals of Sulfadiazine in "Aquaphor" in Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor	
10% Microcrystalline Sulfadiazine in "Aquaphor"	10% Microcrystalline Sulfadiazine in "Aquaphor" and 0.1% "Duponol"
O.D.	O.S.
0.80	3.30
1.50	1.90
0.80	1.80

Specimens of aqueous were withdrawn fifteen minutes after application of the ointment.

It is evident from the data in table 14 that the addition of "duponol" in 0.1 per cent concentration increased the penetration of sodium sulfadiazine in ointment into eyes burned with mustard gas. The addition of the detergent placed the penetration values of sodium sulfadiazine in the realm of the values obtained with sodium sulfacetimide.

The results indicated in tables 2, 10 and 15 again show that, although the ointment base made no significant difference in the penetration of the sulfonamide compound into normal eyes, it did make an important difference in eyes with damaged epithelium. "Aquaphor" does not allow as high aqueous levels to be reached as does the Frieden-

wald-Fuqua type of ointment. It is evident from a comparison of table 15 with table 10 that, although a 5 per cent solution of sodium sulfacetimide gives adequate aqueous concentrations, they are much lower than the levels obtained with the 10 per cent sodium sulfacetimide preparation in the same ointment base.

TABLE 14.—*Influence of Detergent on Penetration of 10 Per Cent Sodium Sulfadiazine in Friedenwald-Fuqua Ointment Base into Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfadiazine per 100 Cc.	
10% Sodium Sulfadiazine in Friedenwald-Fuqua Ointment O.D.	10% Sodium Sulfadiazine in Friedenwald-Fuqua Ointment plus 0.1% "Duponol" O.S.
10.0	34.3
17.5	46.9
19.6	45.0
22.0	40.0
16.0	42.7

TABLE 15.—*Penetration of 5 Per Cent Concentrations of Sodium Sulfacetimide, Calcium Sulfadiazine and Sodium Sulfadiazine in Friedenwald-Fuqua, "Aquaphor" and "Vanisol" Ointment Bases into the Anterior Chamber of Rabbit Eyes Previously Burned with Mustard Gas*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor				
5% Sodium Sulfadiazine in "Vanisol"	5% Calcium Sulfadiazine in "Vanisol"	5% Sodium Sulfacetimide in "Vanisol"	5% Sodium Sulfacetimide in Friedenwald-Fuqua Ointment	5% Sodium Sulfacetimide in "Aquaphor"
2.0	1.9	8.0	6.84	0.680
4.1	2.0	9.4	23.50	0.912
2.9	2.0	6.2	9.30	0.912

TABLE 16.—*Concentrations in Aqueous Humor Fifteen Minutes After Instillation of Four Drops of 5 Per Cent Solutions of Calcium Sulfadiazine, Sodium Sulfadiazine and Sodium Sulfacetimide into Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor		
5% Calcium Sulfadiazine	5% Sodium Sulfadiazine	5% Sodium Sulfacetimide
7.1	15.1	26.0
8.0	10.3	33.0
10.0	9.1	34.7
6.0	12.0	27.8

TABLE 17.—*Results of Application of 10 Per Cent of Sodium Sulfadiazine and 10 Per Cent Sodium Sulfacetimide in Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor			
10% Sodium Sulfacetimide		10% Sodium Sulfadiazine	
O.D. Ointment	O.S. Drops	O.D. Ointment	O.S. Drops
50	120	10	32
42	70	17.6	30.5
63	84	18.6	34.2

Table 17 demonstrates that solutions allow more rapid penetration than ointments.

EVALUATION OF RESULTS

These studies demonstrate that the intraocular penetration of locally applied sulfonamide drugs is influenced by many factors.

The sulfonamide compound itself makes a difference. Sodium sulfamezathine produced the highest intraocular concentrations of sulfonamide in the normal rabbit eye, and sodium sulfacetimide, in the inflamed eye. Microcrystalline preparations did not give rise to significantly higher values than the macrocrystalline forms in the time intervals tested.

The alkaline salt of each sulfonamide compound produced higher intraocular values than the less soluble acid preparation.

The vehicle chosen made a real difference. Solutions allowed more rapid penetration than ointments. Ointments differed in this respect when applied to an inflamed and partially denuded cornea. An oil in water type of base allowed greater intraocular penetration of an inflamed and denuded cornea than did a water in oil type. However, the type of ointment was not an important factor in the presence of a normal cornea. Klein[2f] has shown that an oil in water type of base is a better ointment for intraocular penetration of other drugs, as well as of the sulfonamide compounds.

Although the concentration, 5, 10 or 20 per cent, made no real difference in the presence of a normal cornea, it was significant when the cornea was damaged. The results showed increasing concentrations in the aqueous humor with application of greater concentrations of each sulfonamide drug to the cornea burned with mustard gas.

Detergents increased the intraocular penetration of all sulfonamide compounds, both in the normal and in the inflamed cornea.

Most striking of all factors influencing intraocular penetration of locally applied sulfonamide drugs was the state of the cornea. A multifold increase in penetration occurred with each sulfonamide compound in the presence of an inflamed and partially denuded cornea.

Other factors not included in the experimental studies must be considered in selecting a sulfonamide drug for local administration.

The p_H of the tears usually is about 7.[9] Theoretically, it would be desirable to have a preparation of the same p_H as the tears, other factors being equal. Sodium sulfacetimide in 10 per cent concentration has a p_H of approximately 8, whereas the same concentrations of sodium sulfadiazine, sodium sulfapyridine, sodium sulfathiazole, sodium sulfamerazine and sodium sulfamezathine have a p_H of approximately 10. This may not be an important factor, as the tears have a rapid buffering action. Twenty medical student volunteers who were tested for subjective symptoms with instillation of a solution of 10 per cent sodium sulfadiazine in one eye and 10 per cent sodium sulfacetimide in

9. Feldman, J. P.: p_H and Buffers in Relation to Ophthalmology, Arch. Ophth. **17:** 797 (May) 1937.

the other noted little difference in irritative properties of the two solutions. There were no objective changes. The ammonium salt of sulfadiazine, in 10 per cent concentration, has a p_H of 9.2, and the calcium salt, in 5 per cent concentration, a p_H of 8.5. The calcium salt is not soluble in greater than 5 per cent concentration. There is clinical evidence that the calcium preparation is as efficacious as the sodium salt.[10] This compound could be used if the p_H were a real objection to the utilization of the sodium salt. The same variation in the cation could be applied to other sulfonamide compounds with high p_H values for their sodium salts.

The sulfonamide drugs vary in the concentration required to halt bacterial growth in vitro. Though a drug may be an effective agent in a test tube, it may not be effective in vivo. However, if a drug is ineffective against a certain bacterium in vitro, it most likely will prove unsuccessful in combating a disease caused by that organism. According to in vitro studies with Staphylococcus aureus and Escherichia coli, sulfanilamide is less effective than sulfapyridine, which is about as effective as sulfacetimide. Sulfadiazine and sulfathiazole are more effective than sulfapyridine and sulfacetimide.[11] In other words, it requires much greater concentrations of sulfanilamide than of sulfathiazole to produce a similar bacteriostatic effect on a specific strain of Staph. aureus. Sulfamezathine[12] and sulfamerazine are similar to sulfa-

10. Nelson, C. T., and Spink, W. W.: Calcium Salts of Sulfadiazine and Sulfathiazole, Am. J. M. Sc. **206**:315 (Sept.) 1943.

11. Helmholtz, H. F.: Bacteriostatic Action of Sulfadiazine, Sulfathiazole, Sulfacetimide and Sulfapyridine on Bacteria Isolated from Urinary Infections, Proc. Staff Meet., Mayo Clin. **17**:529 (Oct. 21) 1942. Wyss, O.; Grubaugh, K. K., and Schmelkes, F. C.: Non-Specificity of Sulfonamides, Proc. Soc. Exper. Biol. & Med. **49**:618 (April) 1942. Cohn, A.; Steer, A., and Seijo, I.: Correlation Between Clinical and in Vitro Reactions of Gonococcus Strains to Sulfathiazole, Am. J. M. Sc. **203**:276 (Feb.) 1942. Spink, W. W., and Vivino, J. J.: Sulfonamide-Resistant Staphylococci, J. Clin. Investigation **23**:267 (March) 1944. Rose, F. L.; Martin, A. R., and Bevan, H. G. L.: Sulfamethazine, J. Pharmacol. & Exper. Therap. **77**:127 (Feb.) 1943. Marshall, E. K.; Litchfield, J. I., Jr.; White, H. J.; Bratton, A. C., and Shepherd, R. G.: Comparative Therapeutic Activity of Sulfonamides Against Bacterial Infections in Mice, ibid. **76**:226 (Nov.) 1942. Muir, R. D.; Shamleffer, V. J., and Jones, L. R.: Studies Pertaining to Antibacterial Activity of Sulfathiazole and Its Methyl Derivative, J. Bact. **44**:95 (July) 1942. Organe, E. S., and Polson, M. A.: Comparison of in Vitro Inhibitory Effects and Bacteriostatic Activity, Arch. Int. Med. **70**:777 (Nov.) 1942. White, H. J.: Comparative Activity vs. Coliform Bacteria in Intestines of Mice, Bull. Johns Hopkins Hosp. **71**: 231 (Oct.) 1942. Rammelkamp, C. H.: Present Status of Sulfonamide Therapy, M. Clin. North America **26**:1375 (Sept.) 1942.

12. Schweinburg, F. B., and Yetwin, I. J.: Sulfamethazine, J. Bact. **49**:193 (Feb.) 1945. Rose, F. L.; Martin, A. R., and Bevan, H. G. L.: Sulfamethazine, J. Pharmacol. & Exper. Therap. **77**:127 (Feb.) 1943. Schweinburg, F. B., and Yetwin, I. J.: The in Vitro Action of Sulfamerazine, Phthalylsulfadiazine, Phthalylsulfamerazine and Phthalylsulfathiazole on Enteric Pathogens, New England J. Med. **230**:510 (April 27) 1944.

diazine in this respect. There is evidence that sulfamezathine is more effective than sulfadiazine in vitro against Eberthella typhosa, Esch. coli and varieties of Salmonella.

However, it has been shown that in the ionized form all the sulfonamide compounds mentioned possess similar potency in vitro.[13] That is, at a high p_H range (9 to 10) all sulfonamide compounds have their greatest dissociation and their greatest bacteriostatic activity and are fairly comparable.[14] At neutrality sulfadiazine is more readily dissociated than sulfanilamide, and thus more effective. Nevertheless, at any particular p_H below 9 to 10, a high concentration of sulfanilamide would be more effective against a susceptible strain of Staph. aureus than a very low concentration of sulfadiazine. In other words, for sulfacetimide, sulfanilamide or sulfapyridine to be effective, one should aim for higher concentrations in the infected tissues than are required for sulfadiazine, sulfathiazole or sulfamezathine.

While studying the mechanism of action of sulfanilamide, Woods[15] noted that small amounts of para-aminobenzoic acid would block the antibacterial effects of the compound. This suggests that the antibacterial activity is produced by interference with some metabolic function of the bacterial cell, as para-aminobenzoic acid is an essential growth factor for bacteria. Sulfonamide compounds differ in the quantities of para-aminobenzoic acid required to inhibit their activity. Almost six hundred times as much para-aminobenzoic acid is required to block sulfathiazole as to block sulfanilamide.

Other compounds found in the tissues also interfere with action of the sulfonamide drugs. Examples of these substances are methionine, peptone, aminoacetic acid and the products of tissue autolysis.[16]

Substances such as chloroazodin U.S.P. ("azochloramid") have been incorporated in sulfonamide preparations prepared for local use to enhance the activity of the sulfonamide drug by destroying or binding the inhibitors.[16] Also, maintenance of high p_H values with buffers prevents the great lowering of the p_H that occurs with tissue autolysis. In this way, sulfonamide preparations are kept at higher p_H levels, where they are more dissociated, and thus more active. Urea also aids by re-

13. Schmelkes, F. C.; Wyss, O.; Marks, H. C.; Ludwig, B. J., and Strandskov, F. B.: Mechanism of Sulfonamide Action, Proc. Soc. Exper. Biol. & Med. **50**:145 (May) 1942.

14. Rose, H. M., and Fox, C. L., Jr.: Ionization of Sulfonamides, Proc. Soc. Exper. Biol. & Med. **50**:142 (May) 1942.

15. Woods, D.: The Relation of *p*-Aminobenzoic Acid to the Mechanism of Action of Sulphanilamide, Brit. J. Ophth. **21**:74 (April) 1940.

16. MacLeod, C. M.: Sulfonamides, Ann. New York Acad. **44**:447 (Dec. 14) 1943; Factors Affecting Activity in Therapy of Local Infections, Lectures on Peace and War Orthopedic Surgery, American Academy of Orthopedic Surgeons, Ann Arbor, Mich., Edwards Brothers, Inc., 1943, p. 316.

moval of necrotic tissue. Urea may actually increase the bacteriostatic effects of the sulfonamide compounds.[16]

The antibacterial action of the sulfonamide compounds has been shown to be inhibited by procaine.[17] It is known that procaine can be hydrolyzed, with liberation of free para-aminobenzoic acid by esterases present in human tissues.[18] Fortunately, the local anesthetics used in ophthalmology, such as cocaine, metycaine hydrochloride, tetracaine hydrochloride U.S.P., dibucaine ("nupercaine") hydrochloride and phenacaine hydrochloride U.S.P., show no such inhibition.[19] Dibucaine and phenacaine hydrochloride may actually add antibacterial effect.

Sulfonamide preparations possess a certain toxicity for ocular tissues. There is evidence that they retard regeneration of corneal epithelium.[20] This effect is barely detectable when the sulfonamide preparations are used as drops. However, preparations in ointment or powder base are definitely harmful in this respect. Powders are more dangerous than ointments, and ointments differ in their ability to retard epithelial regeneration. Smelzer found a hydrous wool fat—petrolatum ointment to be less damaging in this respect than the vanishing cream (sodium stearate) type of ointment.

An ideal ophthalmic ointment vehicle for sulfonamide compounds theoretically should retard epithelial regeneration minimally and be an oil in water type, if possible, in order to enhance penetration and maintain an alkaline p_H as an aid in dissociation of the drug. Of course. it should not be irritating, should be of a proper consistency for ease of application and should not disappear too quickly from the conjunctival cul-de-sac.

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17. Peterson, O. L., and Finland, M.: Sulfonamide Inhibiting Action of Procaine, Am. J. M. Sc. **207**:166 (Fe.) 1944.

18. Legge, J. W., and Durie, E. B.: The Antagonism Between Procaine and the Sulfonamides, M. J. Australia **2**:561 (Dec. 26) 1942.

19. Keltch, A. K.; Baker, L. A.; Krahl, H. E., and Clowes, G. H. A.: Anti-Sulfapyridine and Anti-Sulfathiazole Effect of Local Anesthetics Derived from *p*-Aminobenzoic Acid, Proc. Soc. Exper. Biol. & Med. **47**:533 (June) 1941. Landy, M., and Wyeno, J.: Neutralization of Bacteriostatic Activity of Sulfonamides by *p*-Aminobenzoic Acid, ibid. **46**:59 (Jan.) 1941. Lawrence, C. A., and Goetchius, G. R.: The in Vitro Effects upon Sulfonamides of Local Anesthetics Derived from N-Substituted *p*-Aminobenzoic Acids, ibid. **57**:180 (Nov.) 1944. Walker, B. S., and Derow, M. A.: The Antagonism of Local Anesthetics Against the Sulfonamides, Am. J. M. Sc. **210**:585 (Nov.) 1945.

20. Bellows, J. G., and Gluckman, R.: Local Toxic Effects of Sulfanilamide and Its Derivatives, Arch. Ophth. **30**:65 (July) 1943. Berens, C.; deGara, P., and Loutfallah, M.: Effect of Sulfonamide Ointment on Healing of Experimental Wounds, ibid. **30**:631 (Nov.) 1943. Smelser, G. K., and Ozanics, V.: Effect of Chemotherapeutic Agents on Cell Division and Healing of Corneal Burns and Abrasions in Rat, Am. J. Ophth. **27**: 1063 (Oct.) 1944. Leopold, I. H., and Steele, W. H.: Influence of Local Application of Sulfonamide Compounds and Their Vehicles on Regeneration of Corneal Epithelium, Arch. Ophth. **33**:463 (June) 1945.

Attention has been directed recently to "sulfamylon" (para-[aminomethyl]-benzene sulfonamide). It is not inhibited by para-aminobenzoic acid.[21] In 5 per cent concentration, it is more bactericidal in vitro against certain organisms and less toxic than streptomycin, in a concentration of 200 units per cubic centimeter, or than penicillin, in a concentration of 100 units per cubic centimeter. In this concentration it produces no ocular irritation.[22] Measurements of its intraocular penetration have not been reported. Actual trials against experimental and clinical ocular infections have not been made.

There are methods of applying sulfonamide preparations locally other than those mentioned. Iontophoresis and corneal baths produce considerably higher intracorneal levels and concentrations in the aqueous humor than the former methods. The best results in treatment of experimental infections have been attained with iontophoresis. However, these two methods must be used either in the office or in the hospital and require special apparatus. Many patients requiring local application of a sulfonamide preparation can be treated successfully without iontophoresis or corneal bath, particularly when the solutions and ointments containing the drug are properly selected and utilized.

There exists a large literature describing the merits of local application of sulfonamide compounds in treatment of experimental and clinical ocular infections. These articles are concerned mostly with cases of successfully treated conjunctivitis, blepharitis, keratitis and dacryocystitis.[23] It is in such cases that local sulfonamide therapy will continue to be used.

In considering the data listed in table 18, certain suggestions for the choice of a sulfonamide compound for local use may be made. When the cornea is denuded and/or inflamed, apparently any of these drugs will penetrate adequately when applied either as drops or as an ointment. Certainly, the sodium salt of almost any sulfonamide compound will penetrate sufficiently when applied by corneal bath or iontophoresis. The low p_H of solutions of sodium sulfacetimide would appear to be a factor in its favor.

The only criticism that might be raised against the sodium salts of sulfadiazine, sulfapyridine and sulfamerazine is their high p_H in 10 per

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21. Mitchell, G. A. G.; Reese, V. S., and Robinson, C. N.: Marfanil and Marfanil Protalbin, Lancet, **1**:627 (May 13) 1944.

22. Howes, E. L.: Local Chemotherapy of Wounds, Surg., Gynec. & Obst. **83**:1 (July) 1946.

23. Rambo.[2a] Johnstone.[2b] Robson and Scott (footnotes 2*c*, *d* and *e*). Scott and others.[2f] Dickson.[2g] Bellows.[2h] Thygeson.[2j] Thygeson and Braley.[2k] von Sallmann.[2l] Alvaro.[2m] Vorisek.[2n] Simpson, G. V.: Sulfadiazine in Treatment of Dacryocystitis of the Newborn, Arch. Ophth. **33**:62 (Jan.) 1945.

TABLE 18.—*Usefulness of Various Sulfonamide Compounds for Local Therapy of Infections of the Anterior Segment of the Eye*

	Sulfanilamide	Sodium Sulfapyridine	Sodium Sulfacetimide	Sodium Sulfadiazine	Sodium Sulfathiazole	Sodium Sulfamerazine	Sodium Sulfamezathine
Approximate *ph* of 10% solution	.....	10	8	10	10	10	10
Penetration into normal eyes with drops or ointment	Fair	Fair	Fair	Fair	Poor	Fair	Good
Penetration with iontophoresis and corneal bath in normal eyes	Good	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Penetration into eyes with inflamed and denuded corneas of drops or ointment	Very good	Very good	Excellent	Very good	Very good	Very good	Very good
Relative bacteriostatic concentration, mg./100 cc. of medium (Knight's) demanded in vitro against							
Staph. aureus	14.0	3.0	2.0	0.60	0.30	0.6	0.6
Esch. coli	15.0	2.9	2.8	0.65	0.65	0.5	0.5
Experimental evidence of effectiveness against infection of anterior segment, local application	Fair	Fair	Very good	Very good	Very good	No data to date	No data to date
Clinical evidence against ocular infection of anterior segment, local application	Good	Good	Good	Good	Good	No data to date	No data to date

cent concentration and their adequate, but not so high, penetrating values. Because of the high buffering ability of tears, the p_H is not an important objection; and if it were the calcium salts could be used. The lower penetration is also not an objection, as the use of a detergent would insure higher intraocular concentrations. Detergents, however, must be used carefully, as repeated use may lead to superficial, although reparable, corneal damage.[24]

Chemical and experimental data on treatment of ocular infections with sulfamezathine, sulfamerazine and "sulfamylon" are meager. Frequent mention of ocular sensitivity to sulfathiazole occurs in the literature. Therefore, on the basis of available information, the sodium salt of sulfacetimide (now available commercially in 30 per cent concentration) would appear to be the drug of choice, because of its low p_H and great penetrating ability, with sulfadiazine and sulfapyridine following in that order.

SUMMARY

1. The intraocular penetration of locally applied sulfonamide compounds is shown to depend on the following factors: *(a)* the physical form of the compound, *(b)* its solubility, *(c)* the vehicle, *(d)* the presence of a detergent and *(e)* the state of the cornea.

2. Other factors of importance in selecting a sulfonamide compound for local use are considered: *(a)* the p_H of the preparation, *(b)* the bacteriostatic action in vivo, *(c)* the results against standardized experimental ocular infection, *(d)* the results against clinical infection in human eyes and *(e)* the toxicity of the preparation.

3. Suggestions are made as to the best sulfonamide preparation for local ocular use according to the available data.

24. Swan, K. C.: Reactivity of Ocular Tissues to Wetting Agents, Am. J. Ophth. **27:** 1118 (Oct.) 1944. Leopold, I. H.: Local Toxic Effect of Detergents on Ocular Structures, Arch. Ophth. **34**:99 (Aug.) 1945. Irvine, R. S.: Wetting Agents and Detergents, Am. J. Ophth. **29:**1317 (Oct.) 1946.

Smith, Kline & French Laboratories, the Squibb Institute and the Schering Corporation supplied the drugs used in this study.

MIOTIC AND ANTIGLAUCOMATOUS ACTIVITY OF TETRAETHYL PYROPHOSPHATE IN HUMAN EYES

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THE OCULAR effects of a new anticholinesterase chemical, tetraethyl pyrophosphate, have been investigated in several subjects with normal eyes and in several patients with glaucomatous eyes. Although the number of observations is small, the information obtained appears to be adequate for a qualitative characterization of the actions of this compound. A more quantitative experimental comparison of tetraethyl pyrophosphate with physostigmine and di-isopropyl fluorophosphate (DFP) and a clinical comparison with di-isopropyl fluorophosphate in glaucomatous and in atropinized eyes are to be reported subsequently.[1]

Tetraethyl pyrophosphate is a colorless, water-soluble and lipid-soluble, hygroscopic liquid of low volatility. It is the principal active ingredient of a more complex substance, commercial hexaethyl tetraphosphate (tri-diethyl phosphophosphate), which, because of strong nicotine-like action, was used in Germany during the war as an insecticide, substituting for natural nicotine, under the name of "bladan."[2] Tetraethyl pyrophosphate is being used increasingly in this country for the same purpose, under the name of "nifos." Pure tetraethyl pyrophosphate has several times as great biologic activity as has commercial hexaethyl tetraphosphate, but both substances are highly toxic to warm-blooded animals and produce extreme miosis. In the present investigation, the pure tetraethyl pyrophosphate has received principal attention.[3]

The few studies on the biologic action of tetraethyl pyrophosphate or of hexaethyl tetraphosphate which have thus far been published show that both compounds are highly effective inhibitors of cholin-

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From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1. *(a)* Cogan, D. G., and Grant, W. M.: To be published. *(b)* Dunphy, E. B., and Grant, W. M.: To be published.

2. Hall, S. A., and Jacobson, M.: Hexaethyl Tetraphosphate and Tetraethyl Pyrophosphate: Chemical and Physical Properties, Indust. & Engin. Chem., **40**:694-699, 1948.

3. The tetraethyl pyrophosphate and hexaethyl tetraphosphate were supplied by Dr. J. S. Harris, of the Monsanto Chemical Company, St. Louis.

esterases; in fact, tetraethyl pyrophosphate is usually effective at lower concentrations than is physostigmine or di-isopropyl fluorophosphate.[4] The lethal dose of systemically administered hexaethyl tetraphosphate and tetraethyl pyrophosphate in experimental animals is comparable to that of physostigmine.[5] Ready penetration of the skin by hexaethyl tetraphosphate and tetraethyl pyrophosphate is indicated by a high lethal effectiveness after application to animal's skin.[5b] A certain facility of penetration of these compounds into the eye, consistent with their known miscibility in water or oil, is suggested by reports of extreme miosis in rabbit eyes promptly following application of dilute solutions of hexaethyl tetraphosphate.[6] Application of tetraethyl pyrophosphate in bland vehicles to the eyes of rabbits and guinea pigs likewise produces temporary maximum miosis without observable injury to the eyes.[1] In fact, even pure tetraethyl pyrophosphate is not damaging to the corneal epithelium, as judged by usual clinical standards.

The notable properties of cholinesterase-inhibiting action and ready penetration into the eye without injury suggested the possible usefulness of tetraethyl pyrophosphate in the treatment of glaucoma on the same basis as treatment with physostigmine or di-isopropyl fluorophosphate. Accordingly, an assessment of the action of tetraethyl pyrophosphate on human eyes was undertaken.

OBSERVATIONS ON NORMAL HUMAN EYES

For a preliminary estimate of the effectiveness of tetraethyl pyrophosphate as a miotic in the human eye, the minimal effective concentration for production of perceptible miosis was determined in several subjects. Observations were made using aqueous saline solution, peanut oil, purified kerosene and liquid petrolatum as vehicles. In the case of aqueous solutions, freshly mixed preparations were used, for tetraethyl pyrophosphate in water loses half its biologic activity in approximately seven hours at room temperature.[2] In all tests, a drop of solution was placed in the conjunctival sac of one eye with the head held back and the lids held apart for approximately twenty seconds, whereas the companion eye was untreated and served as a control. Differences

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4. *(a)* DuBois, K., and Mangun, G. H.: Effect of Hexaethyl Tetraphosphate on Choline Esterase in Vitro and in Vivo, Proc. Soc. Exper. Biol. & Med. **64**:137-141, 1947. *(b)* Brauer, R. W.; Hodge, H. C., and Ravin, H. A.: The Inhibition of Cholinesterase Activity of Human and Canine Blood Plasma and Erythrocytes by Certain Phosphate Esters, Federation Proc. **6**:311, 1947. *(c)* Mangun, G. H., and DuBois, K. P.: Toxicity and Mechanism of Action of Tetraethyl Pyrophosphate, ibid. **6**:353, 1947. *(d)* Koppanyi, T.; Karczmar, A. G., and King, T. O.: Effect of Tetraethyl Pyrophosphate on Sympathetic Ganglionic Activity, Science **106**:492, 1947.

5. *(a)* Hagan, E. C., and Woodward, G.: Toxicological Properties of Hexaethyl Tetraphosphate, Federation Proc. **6**:335, 1947. *(b)* Deichmann, W. B., and Witherup, S.: The Immediate Toxicity of Hexaethyl Tetraphosphate, Tetraethyl Pyrophosphate and Hexaoctyl Tetraphosphate to Rabbits and Rats, ibid. **6**:322, 1947.

6. DuBois and Mangun.[4a] Koppanyi and others.[4d]

in pupillary size were determined periodically by inspection, and measurements were made with a standard entoptic pupillometer. The results of a series of such measurements are shown in the table, with those of similar measurements made using physostigmine sulfate and di-isopropyl fluorophosphate in 0.9 per cent solution of sodium chloride for purposes of comparison.

The data in the table indicate that the threshold concentration for miosis in human beings is of the same order for tetraethyl pyrophosphate as for physostigmine and di-isopropyl fluorophosphate when all are compared with the use of a common solvent, 0.9 per cent solution of sodium chloride. The data also indicate that tetraethyl pyrophosphate is absorbed with approximately equal effectiveness from a saline and from a peanut oil solution.

In these studies, the maximum concentration of tetraethyl pyrophosphate as applied to the normal human eye was 0.1 per cent in saline solution, which caused no immediate discomfort, but within three minutes provoked twitching of the lids and within seven minutes produced a difference in pupillary size of 1.5 mm. with moderate spasm

Minimum Concentration of Drug Which Produced a Perceptible Difference in Pupillary Size

Tetraethyl pyrophosphate	
In peanut oil, 0.005%	(0.5 mm. miosis in 1 of 2 subjects)
In purified kerosene, 0.001%	(0.5 mm. miosis in 3 of 8 subjects)
In liquid petrolatum, 0.010%	(0.75 mm. miosis in 1 subject)
In 0.9% sodium chloride, 0.003%	(1 mm. miosis in 1 of 2 subjects)
Physostigmine sulfate	
In 0.9% sodium chloride, 0.001%	(0.5 mm. miosis in 1 subject)
Di-isopropyl fluorophosphate	
In 0.9% sodium chloride, 0.005%	(0.5—1 mm. miosis in 2 subjects)

of accommodation for near vision. A maximum relative miosis of 2.25 mm. with pronounced spasm of accommodation and aching of the eye and brow was present within fifteen minutes. At that time ocular tension was equivalent to 21 mm. of mercury, the same as that in the companion, control, eye. Accommodation returned to normal only after four days, and relative miosis persisted for more than three weeks, although the difference in pupillary size was only 0.75 mm. at the end of five days.

Eyes which received 0.01 per cent tetraethyl pyrophosphate, irrespective of the vehicle, showed within thirty minutes an average difference in pupillary size of 1 mm., with no conspicuous disturbance of accommodation. In most instances an anisocoria persisted for twenty-four hours after this dose of tetraethyl pyrophosphate. Some of the eyes which received miotic concentrations of the drug showed slight transient engorgement of conjunctival vessels. No discomfort from application of the drops was experienced, and there was no evidence of corneal damage at any time.

OBSERVATIONS ON GLAUCOMATOUS HUMAN EYES

It was concluded from the observations on the effect of tetraethyl pyrophosphate on normal animal and human eyes that this drug might reasonably be tested on glaucomatous human eyes in concentrations as great as 0.1 per cent. Of the vehicles employed in the previous tests, it was concluded that peanut oil was most suitable for use with patients, since this vehicle permitted good absorption, caused no discomfort and was favorable to the stability of the compound. Purified kerosene was not chosen for this purpose, in spite of its apparent superiority with respect to absorption of tetraethyl pyrophosphate, only because some subjects noted a slightly unpleasant odor and taste after the application of this vehicle to the eye.

Of the patients on whom tetraethyl pyrophosphate was tried, 1 had absolute glaucoma; 4, secondary glaucoma; 9, chronic simple glaucoma, and 1, glaucoma with congenital aniridia. In most instances, trial of tetraethyl pyrophosphate was made after control of tension by means of other miotics had been found unsatisfactory.

DESCRIPTION OF CASES

CASE 1.—C. F., aged 85, had absolute glaucoma of indeterminate duration in one eye, with tension of approximately 80 mm., which was uninfluenced by pilocarpine, methacholine and neostigmine. Tension was also unaffected by 0.1 per cent tetraethyl pyrophosphate or hexaethyl tetraphosphate, applied two to four times a day. When tetraethyl pyrophosphate was used more than twice a day, aching of the eye and brow was noted.

CASE 2.—Z. H., aged 75, with cataract, exfoliation of the capsule and glaucoma in the right eye, and glaucoma following intracapsular cataract extraction in the left eye, had had cyclodialysis, paracenteses and trephination on the left eye but no surgical treatment of the right eye. During the preceding ten months, 4 per cent pilocarpine nitrate had been used four to six times a day in both eyes, the tension remaining in the neighborhood of 30 mm. in the right eye and 40 mm. in the left. When medication was changed to use of 0.1 per cent tetraethyl pyrophosphate in both eyes twice a day for three weeks, the tension remained the same in the right eye and decreased only to approximately 35 mm. in the left eye. The patient's only complaint in regard to the use of tetraethyl pyrophosphate was blurring and dimness of distance vision.

CASE 3.—E. F., aged 21, had had tension of about 60 mm. most of the time during six months following discission of a pupillary membrane due to an earlier traumatic cataract in one eye, the increased tension persisting in spite of trephination, iridotomy, iridectomy, paracentesis and use of 4 per cent pilocarpine nitrate. During treatment with 0.1 per cent tetraethyl pyrophosphate twice a day for two weeks, the tension varied from 45 to 48 mm. The conjunctival vessels became considerably congested, but the aqueous remained clear.

CASE 4.—A. G., a Negro aged 67, with neurosyphilis and primary atrophy of the optic nerve in one eye, had glaucoma with attacks of uveitis in the other eye. During the past three months the tension had stayed in the high forties in spite of treatment

at different times with pilocarpine, methacholine and neostigmine, atropine, epinephrine and carbachol ("doryl"). Trial of 0.1 per cent tetraethyl pyrophosphate twice a day for four days also produced no change in tension.

CASE 5.—L. G., aged 72, had glaucoma in one eye following a complicated cataract extraction. Under treatment with miotics, definite sensitivity to pilocarpine, methacholine with neostigmine, and probably also to physostigmine, appeared. A cyclodialysis was done, after which the tension was maintained in the forties with use of 4 per cent pilocarpine nitrate, in the thirties with carbachol and in the high twenties with methacholine and neostigmine, all used four times a day. Because of the multiple sensitivities, trial was made of 0.05 per cent tetreathyl pyrophosphate twice a day for a month. With this drug, the itching, conjunctivitis and dermatitis rapidly disappeared, the patient had no unpleasant symptoms and the tension was maintained at 18 mm.

CASE 6.—M., aged 41, had chronic simple glaucoma in both eyes, which had been treated by trephination. The anterior chambers were extremely shallow. No miotic was required for the right eye, while 2 per cent pilocarpine nitrate maintained the tension at about 30 mm. in the left eye. A trial use of 0.1 per cent tetraethyl pyrophosphate in the left eye three times in one day was followed by a rise of tension to 46 mm., with rapid return to 30 mm. on resumption of pilocarpine nitrate. In order to determine whether the rise in tension had been due to an untoward effect of tetraethyl pyrophosphate or to insufficient miotic action, several days later two applications of 0.1 per cent tetraethyl pyrophosphate were made, in addition to the regular administration of pilocarpine. A temporary rise of tension to 58 mm. resulted. On both occasions on which the tension increased, the anterior chamber became extremely shallow, but no cells or flare could be seen in the aqueous.

CASE 7.—S. H., a Negro aged 64, had chronic simple glaucoma in both eyes, for which no operation had been performed. Tensions were maintained in the middle thirties with use of 4 per cent pilocarpine nitrate five times a day. A trial use of 0.1 per cent di-isopropyl fluorophosphate once a day had brought the tension to 21 mm., but the drug could not be tolerated by the patient on account of severe headaches, facial pain and nausea. Again, with pilocarpine nitrate, as well as with the addition of 0.75 per cent carbachol, tension was in the thirties. Trial instillations of 0.1 per cent tetraethyl pyrophosphate twice a day normalized the tension but caused considerable headache. With the use of 0.05 per cent tetraethyl pyrophosphate twice a day for a month, only occasional mild headache was noted, and tension was kept in the low and middle twenties. On two occasions, substitution of applications of an ointment containing 0.25 per cent physostigmine sulfate twice a day for five day periods was made for purposes of comparison, and tensions of between 27 and 31 mm. were found.

CASE 8.—W. S., a Negro aged 69, had chronic simple glaucoma in both eyes, for which no operation had been performed. Tension (without treatment) was 48 mm.; with use of 4 per cent pilocarpine nitrate four times a day, it was about 30 mm. With instillations of pilocarpine continued in one eye and use of 0.1 per cent tetraethyl pyrophosphate twice a day in the other eye for five weeks, the tension was kept in the middle twenties in both eyes. The patient noted blurring of vision and headache the first few times the drug was used, but not thereafter.

CASE 9.—R. L., aged 80, had chronic simple glaucoma in both eyes, for which no operation had been performed. With use of 4 per cent pilocarpine nitrate three times a day, tension was about 30 mm. On administration of 0.1 per cent tetraethyl pyrophosphate twice a day for two days, the tension became 20 mm., but on account of headache and blurred vision, the use of pilocarpine was resumed, with return of tension to the original level.

CASE 10.—D. A., aged 82, had chronic simple glaucoma in her only eye, in which tension was in the high thirties and had not been materially altered by treatment at different times during a year with 4 per cent pilocarpine nitrate, 1.5 per cent carbachol, 0.1 per cent di-isopropyl fluorophosphate or methacholine chloride and neostigmine sulfate. Permission for operation was refused, and tension rose to 48 mm. on use of pilocarpine. The eye was white, the pupil small and the anterior chamber moderately shallow. One drop of 0.1 per cent tetraethyl pyrophosphate was instilled, and twenty minutes later the tension was 65 mm., without appearance of congestion. Treatment was continued with pilocarpine and physostigmine.

CASE 11.—J. M., aged 78, had absolute glaucoma in one eye; in the other eye there was cataract with exfoliation of the lens capsule and glaucoma, for which operation was refused, although the tension had varied from 30 to 50 mm. during a year of medication with 4 per cent pilocarpine nitrate. The anterior chamber was deep. Without medication the tension was 62 mm., but with 1 drop of 0.1 per cent tetraethyl pyrophosphate it was brought to 37 mm. in an hour. On a regimen of 0.05 per cent tetraethyl pyrophosphate twice a day, the tension was maintained between 34 and 40 mm., with no discomfort.

CASE 12.—E. C., aged 67, had chronic simple glaucoma in both eyes. With use of 4 per cent pilocarpine nitrate every four hours and 0.25 per cent physostigmine sulfate ointment at night, control of tension was good in one eye and inadequate (varying around 30 mm.) in the other. The anterior chamber was very shallow in both eyes. With use of 0.1 per cent tetraethyl pyrophosphate three times a day, the tensions were maintained at essentially the same level as with the previous medication.

CASE 13.—B. C., aged 37, had had chronic simple glaucoma and repeated attacks of high tension, with dystrophy of the corneal endothelium and epithelial edema in one eye, for approximately three years. A trephination was done, but for nine months the tension had remained in the thirties in spite of treatment with 4 per cent pilocarpine nitrate and with epinephrine. Medication with 0.1 per cent hexaethyl tetraphosphate four times a day brought the tension within normal limits, and there was no discomfort. Trial treatment with 0.05 per cent tetraethyl pyrophosphate caused aching about the eye, but with use of a 0.025 per cent solution three times a day for six weeks the tension was kept between 13 and 25 mm., with no further discomfort except that from bullous keratitis, which had progressed despite the lowered tension.

CASE 14.—M. L., aged 38, had chronic simple glaucoma, congenital coloboma of the iris and choroid and cataract in both eyes. Without treatment the tension was in the neighborhood of 40 mm., while with use of 4 per cent pilocarpine nitrate, in addition to 1.5 per cent carbachol, several times a day it was in the high thirties. With 0.05 per cent tetraethyl pyrophosphate instilled three times a day, the tension was kept in the neighborhood of 20 mm. or lower, and no discomfort was experienced.

CASE 15.—F. B., aged 5 years, had congenital nystagmus, aniridia, partial dislocation of the lens and tension of 30 to 40 mm. in both eyes, with or without use of 2 per cent pilocarpine nitrate three times a day. One eye was then treated with 0.1 per cent tetraethyl pyrophosphate twice a day, giving a tension of 17 mm. (under ether). For comparison, the other eye was treated simultaneously with 0.25 per cent physostigmine sulfate ointment twice a day, giving a tension of 21 mm. (under ether). When miotics were discontinued for several days, the tensions became 32 and 30 mm. (under ether), respectively.

COMMENT

Practically all patients for whom tetraethyl pyrophosphate was tried were examined on several occasions with the slit lamp biomicroscope, usually several days after treatment with the drug was begun.

No corneal damage was observed, nor was any perceptible aqueous flare or increase of cells in the aqueous observed to follow the use of the drug. The patient (case 6) who had the definite rise in tension following instillation of tetraethyl pyrophosphate on two occasions was examined twenty-four hours later, when the aqueous appeared normal. In an additional case, not reported here, in which tetraethyl pyrophosphate was used during convalescence from cyclodiathermy, the postoperative reaction subsided, and the aqueous became normally clear without delay. In no instance were systemic symptoms noted from application of tetraethyl pyrophosphate to the eye in the doses employed in the present study.

CONCLUSIONS

From the observation reported here, it appears that tetraethyl pyrophosphate is effective as a miotic in the normal human eye in concentrations comparable to effective concentrations of physostigmine or di-isopropyl fluorophosphate. The duration of miosis induced with tetraethyl pyrophosphate is intermediate between that with physostigmine and that with di-isopropyl fluorophosphate.

In the treatment of glaucoma, tetraethyl pyrophosphate appears to be most effective in patients who respond appreciably to standard miotic drugs, such as pilocarpine, e. g., with lowering of their ocular tensions to the thirties. In several instances, lowering of tension was more effective at a dosage level of 0.05 to 0.1 per cent tetraethyl pyrophosphate twice a day than with use of 4 per cent pilocarpine nitrate several times a day. Comparison with physostigmine has not been adequately made, but in a case of chronic simple glaucoma (case 7) and in another of glaucoma with aniridia (case 15) an impression was obtained of some superiority of the drug over 0.25 per cent physostigmine sulfate ointment used twice a day. It is apparent from experience in case 5 that tetraethyl pyrophosphate may be used for patients who have sensitivities to other miotics.

Disadvantages of tetraethyl pyrophosphate which are shared in as yet undetermined degree with other anticholinesterase miotics, such as di-isopropyl fluorophosphate and physostigmine, are, most commonly, the symptoms of spasm of accommodation for near vision, dimness of vision and aching of the eye, particularly with excessive doses. These complaints appear to be usually absent or slight with administration of 0.05 per cent tetraethyl pyrophosphate twice a day, especially after the first few days of use, but may be pronounced with the 0.1 per cent solution, especially if this dose is administered more than twice a day. Less commonly, a rise in tension may be produced by tetraethyl pyro-

phosphate in certain eyes, as noted in cases 6 and 10. The features which may distinguish eyes responding in this way from other eyes have not been determined, but the extremely shallow chambers present in the case (6) in which rise in tension was most definitely due to tetraethyl pyrophosphate is suggestive of a mechanical predisposing factor. However, in other cases in which definitely shallow chambers were present (e. g., case 12) the eye did not respond to the drug in this way.

SUMMARY

Tetraethyl pyrophosphate is comparable to physostigmine and di-isopropyl fluorophosphate in miotic activity in normal human eyes and is effective in lowering the tension in glaucomatous human eyes in which there is an appreciable response to standard miotics. Tetraethyl pyrophosphate may be used when there is local sensitivity to other miotics. In several instances, more effective lowering of tension has been obtained from administration of 0.05 to 0.1 per cent tetraethyl pyrophosphate in peanut oil twice a day than from use of 4 per cent pilocarpine nitrate several times a day. An excessive dose of tetraethyl pyrophosphate may cause aching about the eye, and in certain eyes the drug may cause an increase in tension.

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EFFECT OF INSULIN HYPOGLYCEMIA ON THE CILIARY MUSCLE

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Ever since the introduction of insulin in the treatment of diabetes mellitus by Banting and Best, extensive studies have been made to determine the exact mode of action of insulin. Insulin lowers the blood sugar and stimulates the formation of glycogen in the liver. Recently, Price, Cori and Colowick[1] have found one fundamental function of insulin. They have demonstrated that the action of the enzyme hexokinase, which with adenosine triphosphate converts glucose to glucose-6-phosphate, may be inhibited in vivo or in vitro by anterior pituitary N. F. and that this inhibition can be counteracted by insulin.

In contrast to the action of insulin, anterior pituitary results in hyperglycemia and glycosuria. Another antagonist to insulin in the maintenance of the blood sugar level is epinephrine, which increases the blood sugar by mobilizing sugar from glycogen. When insulin is given in excess, changes in distribution of lipids and loss of chromaffin substance in the adrenal glands are found in various animals. This can be prevented by injections of epinephrine.[2] There is an increase of epinephrine in the circulating blood during insulin hypoglycemia.[3] Clinical and experimental evidences of increased secretion of epinephrine during insulin hypoglycemia are acceleration of the heart rate, dilatation of the pupils, flushing of the face and periodic apparent exophthalmos, with retraction of the lid in some stages.

Submitted as candidate's thesis in partial fulfilment of the requirements for membership in the American Ophthalmological Society, 1947.

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3. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenalin Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924. Tietz, E. B.; Dornheggen, H., and Goldman, D.: Blood Adrenalin Levels During Insulin Shock Treatments for Schizophrenia, Endocrinology **26**:641, 1940.

In some stages of insulin hypoglycemia there are pinpoint pupils, pallor and salivation, all evidences of stimulation of the parasympathetic nervous system. During insulin hypoglycemia gastric secretion and motility are increased, and this increase can be inhibited by atropine or by section of the vagus nerve.[4] Poos[5] stated that Scheiner's test reveals an irritable condition of the ciliary muscle after injection of insulin. Schmidt[6] found that insulin caused no alteration in the equilibrium of the vegetative nervous system in any direction, and he observed no change in the refraction of the eye before, during or after insulin hypoglycemia.

The action of insulin is not yet fully understood. As the blood sugar falls after the administration of a large dose of insulin, many and varied signs and symptoms appear. Insulin hypoglycemia resembles anoxia and asphyxia in many ways.[7] It is difficult to determine whether the signs and symptoms are due to direct action of insulin, to hypoglycemia, to a lowered metabolism of the brain or to substances poured into the blood stream to counteract the insulin and raise the blood sugar. The symptoms vary at different stages of shock and in different types of persons.

PRESENT INVESTIGATION

This study was made on patients treated with insulin hypoglycemia for schizophrenia and other psychoses. This therapy is commonly called insulin shock although the patients do not go into true shock. Retinoscopic examinations were made before and during each treatment. A streak retinoscope at a distance of 1 meter was used. The following drugs were used individually to produce mydriasis or mydriasis and cycloplegia: 1 per cent paredrine hydrobromide ophthalmic,[8] 4 per cent; homatropine hydrobromide and 1 per cent atropine sulfate. The paredrine was instilled every ten minutes for six doses; the homatropine, every ten minutes for five doses, and the atropine, three times a day for three days.

There were no cases of delayed recovery. Usually the treatment was terminated by giving dextrose by stomach tube and occasionally by intravenous injection. The blood sugar, which was measured by the Folin-Wu method, varied from 21 to 60 mg. per hundred cubic centimeters. The depth of shock did not depend so much on the level

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4. Quigley, J. P.; Johnson, V., and Solomon, E. I.: Action of Insulin on the Motility of the Gastro-Intestinal Tract, Am. J. Physiol. **90**:89, 1929.

5. Poos, F.: Augenerscheinungen bei erblichen Schwankungen des Blutzuckers, Klin. Monatsbl. f. Augenh. **84**:103, 1930.

6. Schmidt, R.: Insulinshock und Auge, Nervenarzt **11**:615, 1938.

7. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System: Basis for Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

8. Paredrine hydrobromide ophthalmic is a 1 per cent solution of *p*-hydroxy-a-methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved in merthiolate, 1:50,000.

of the blood sugar as on how long the blood sugar had been at a low level. There was a great variation in the reaction of patients to insulin. The retinoscopic examinations were made between two and three and one-half hours after the injection of insulin. The term "light wet shock" is used to denote a patient who is perspiring profusely but who can be aroused and answer questions; "deep wet shock," a patient who cannot be aroused and who will need to have dextrose administered by stomach tube or intravenously to bring him out of shock.

The refractive error, as found by retinoscopic examination, was translated into the spherical equivalent by adding the spherical and one-half the cylindrical value algebraically. The astigmatic error did not vary much unless it was necessary to hold the eyelids open for examination during shock.

With paredrine as a mydriatic, there was an increase in refractive power in 19 eyes during the shock period as compared with that determined by retinoscopic examination before shock. When the refractive power of an eye is increased, stronger minus lenses or weaker plus lenses are needed to correct the refractive error. Decreased refractive power (weaker minus lenses or stronger plus lenses) was found in 6 eyes. There was no change in 3 eyes. The increased refractive power varied from —0.12 to —2.12 D. The decreased refractive power varied from +0.12 to +0.62 D. The average change was —0.53 D. This value was determined by adding all the changes algebraically and dividing the sum by the number of eyes tested. It was impossible to examine 1 patient during shock because the pupils could not be dilated with paredrine. The day before, without insulin, the pupils had dilated readily with paredrine, and the next day they dilated during shock with homatropine.

Of the eyes receiving homatropine cycloplegia, 28 showed increased refractive power varying from —0.12 to —1.12 D. during shock. Twelve eyes showed decreased refractive power varying from +0.12 to +0.75 D. Ten eyes showed no change. The average change was —0.16 D.

In the eyes receiving atropine cycloplegia, 5 eyes showed increased refractive power varying from —0.12 to —0.37 D. during shock. Ten eyes showed decreased refractive power varying from +0.12 to +0.50 D. Five eyes showed no change. The average change was +0.09 D.

If the patients are classified according to age, depth of shock and type of mydriatic used, striking differences are found. Patients over 40 years of age were not given atropine and were not allowed to go into deep wet shock.

In table 3 are listed all the changes in spherical equivalent, expressed in diopters, classified according to the type of mydriatic and the depth of shock. They are listed in order, from the greatest stimulation to the greatest relaxation of the ciliary muscle. The median is shown for each group.

TABLE 1.—*Data on Changes in Refractive Power After Insulin Hypoglycemia of 30 Patients*

Case No.	Age Yr.	Sex	Insulin Dose, Units	Time, Hr.	Degree of Shock*	Change in Spherical Equivalent. D. Paredrine Hydrobromide	Homatropine	Atropine
1	25	F	140	3½	DWS (36 mg. 100 cc.)		OD −1.12 OS −0.62	
			130	2½	DWS		OD +0.37 OS +0.75	
			140	2½	DWS		OD 0 OS +0.50	
			140	2½	DWS	OD −1.87 OS −2.12		
2	30	F	140	2½	DWS (39.6 mg. 100 cc.)		OD −0.56 OS −0.62	
			140	2½	LWS		OD 0 OS 0	
			140	2½	DWS	OD −1.62 O,S −1.50		
3	28	M	150	3	LWS (33 mg. 100 cc.)		OD −0.25 OS −0.25	
			200	3	DWS	Pinpoint Pupils		
4	51	M	20	3	LWS	OD +0.50	OS +0.50	
5	41	F	30	2½	LWS		OD −0.50 OS 0	
			140	2½	LWS		OD +0.12 OS +0.12	
			190	2½	LWS	OD −0.62	OS 0	
6	38	M	330	2	LWS		OD 0 OS 0	
			180	3	LWS	OD 0	OS −0.12	
7	28	M	150	2½	DWS	OD −1.00	OS −1.00	
			160	2½	DWS			OD +0.25 OS +0.25
8	33	F	110	2½	LWS	OD −0.12	OS +0.25	
			120	2½	DWS			OD +0.25 OS +0.25
9	36	M	100	2½	LWS		OD +0.37 OS +0.37	
			90	2½	DWS	OD −1.00	OS +0.25	
10	23	F	20	3	LWS		OD −0.25 OS 0	
			90	2½	LWS		OD −0.12 OS 0	
			90	2½	DWS	OD −1.50	OS +0.12	
11	34	F	100	2½	LWS	OD +0.62	OS −0.37	OD −0.12 OS −0.12
			70	2½	LWS			
12	31	F	20	3	Very light	OD −0.25	OS −0.25	
			230	2½	LWS (27 mg. 100 cc.)	OD −0.50	OS −0.37	
13	49	F	160	3	LWS	OD +0.37 OS +0.37		
14	33	F	80	2½	DWS (30 mg. 100 cc.)	OD +0.18	OS −0.18	
15	15	M	170	2½	LWS	OD +0.12	OS 0	
			180	3	DWS			OD +0.37 OS +0.50
16	21	M	110	3	Very light	OD −0.06		OS +0.37
17	19	M	100	2	LWS	OD −0.75		OS 0
18	20	F	100	2½	LWS	OD −0.50		OS 0
19	36	F	60	3	LWS	OD −0.12		OS 0
20	36	F	220	3	LWS	OD 0		OS 0
21	22	F	210	3	LWS	OD −0.75		OS −0.12
22	24	M	150	3	LWS	OD 0		OS −0.25
23	21	M	100	2	LWS	OD −1.75		OS −0.37
24	20	M	280	2½	DWS	OD −0.75		OS 0
25	25	F	180	2½	LWS	OD −0.25		OS +0.25
26	15	M	250	2½	LWS			OD +0.25 OS +0.12
27	31	F	70	2½	DWS (33 mg. 100 cc.)		OD −0.75 OS −0.50	
			40	3	DWS		OD −0.37 OS −0.12	

28	31	F	130	2½	DWS (27 mg. 100 cc.)	OD −0.25 OS −0.12
			100	2½	DWS	OD −0.25 OS −0.50
29	35	F	50	2	LWS	OD −0.62 OS −0.50
			60	3	DWS	OD −0.50 OS −0.50
30	17	F	40	2½	Very light	OD −0.37 OS +0.12

*DWS indicates deep wet shock; LWS, light wet shock.

TABLE 2.—*Effect of Age, Depth of Insulin Hypoglycemia and Type of Mydriatic on Refractive Power*

Group	Age, Yr.	No. of Eyes	Depth of Shock*	Mydriatic or Cycloplegic	Average Change in Refraction, D.
1	15-30	7	DWS	Paredrine†	−1.48
2	15-30	8	LWS	Paredrine	−0.50
3	31-40	2	DWS	Paredrine	−0.41
4	31-40	12	DWS	Homatropine	−0.31
5	15-30	10	DWS	Homatropine	−0.21
6	31-40	11	LWS	Homatropine	−0.11
7	15-30	11	LWS	Homatropine	−0.10
8	31-40	4	LWS	Atropine	−0.06
9	31-40	7	LWS	Paredrine	−0.05
10	15-30	9	LWS	Atropine	−0.03
11	41-51	6	LWS	Homatropine	+0.04
12	41-51	4	LWS	Paredrine	+0.15
13	31-40	2	DWS	Atropine	+0.25
14	15-30	5	DWS	Atropine	+0.27

*DWS indicates deep wet shock; LWS, light wet shock.
†Paredrine hydrobromide ophthalmic was used.

TABLE 3.—*Changes in Spherical Equivalent, Classified According to Type of Mydriatic and Depth of Shock**

Paredrine Hydrobromide Ophthalmic		Homatropine Hydrobromide		Atropine Sulfate	
Deep	Light	Deep	Light	Deep	Light
−2.12	−1.75	−1.12	−0.62	0	−0.37
−1.87	−0.75	−1.00	−0.50	+0.25	−0.25
−1.62	−0.75	−0.75	−0.50	+0.25	−0.12
−1.50	−0.62	−0.62	−0.37	+0.25 Median	−0.12
−1.50 Median	−0.50	−0.62	−0.37	+0.25	−0.12
−1.00	−0.50	−0.56	−0.37	+0.37	0
−1.00	−0.25	−0.50	−0.25	+0.50	0 Median
−0.75	−0.25	−0.50	−0.25		0
+0.18	−0.12	−0.50	−0.25		0
	−0.12 Median	−0.50	−0.25		+0.12
	−0.06	−0.37 Median	−0.12		+0.25
	0	−0.25	−0.12		+0.25
	0	−0.25	0		+0.37
	0	−0.18	0 Median		
	+0.12	−0.12	0		
	+0.37	−0.12	0		
	+0.37	0	0		
	+0.50	+0.12	0		
	+0.62	+0.25	0		
		+0.37	0		
		+0.50	0		
		+0.75	+0.12		
			+0.12		
			+0.12		
			+0.25		
			+0.37		
			+0.37		
			+0.50		

*"Deep" and "light" indicate deep and light wet shock. Spherical equivalents are expressed in diopters.

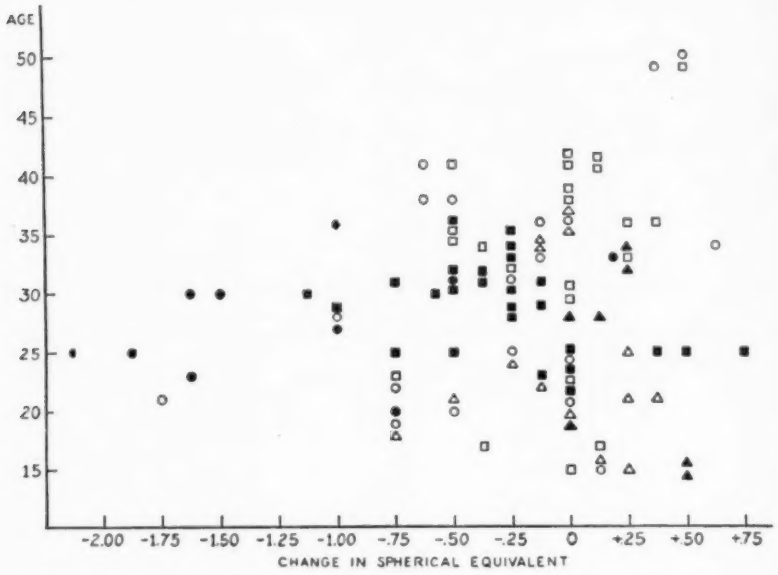

Chart 1.—Changes in spherical equivalent classified according to age, type of mydriatic and depth of shock.

In this chart and in chart 3, circles show values with paredrine hydrobromide mydriasis during light wet shock (clear circles) and during deep wet shock (solid circles); squares, values for homatropine cycloplegia during light wet shock (clear squares) and during deep wet shock (black squares), and triangles, values for atropine cycloplegia during light wet shock (clear triangles) and during deep wet shock (solid triangles).

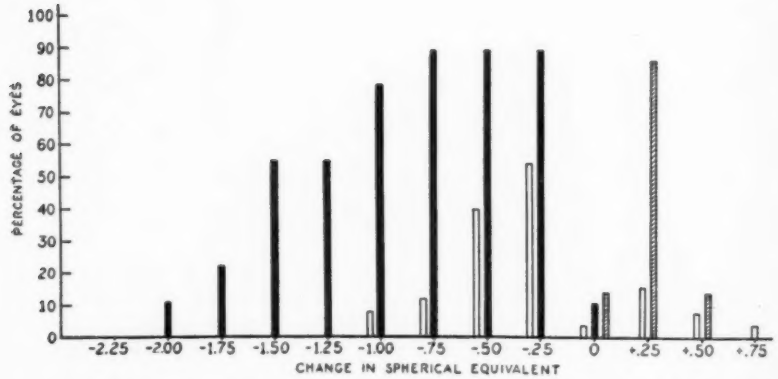

Chart 2.—Percentage of eyes having as much as or more than the indicated change in spherical equivalent. For example, 89 per cent of the eyes under paredrine mydriasis during deep wet shock had a change as much as or more than 0.25 D., while only 11 per cent had as much stimulation as —2.00 D.

COMMENT

It can be seen from the tables and charts that some of the patients with paredrine mydriasis had definite stimulation of the ciliary muscle and accommodation during insulin hypoglycemia, even up to 2 D. This was most evident in the youngest group and patients deepest in shock. Patients 20 to 30 years of age are easiest to throw into shock; the youngest patients have the greatest power of accommodation.

With homatropine cycloplegia a smaller percentage of eyes showed ciliary stimulation, and to a lesser degree, than with paredrine mydriasis. With atropine cycloplegia a still smaller percentage of eyes showed ciliary stimulation, and to a much less degree, than with homatropine cycloplegia. Some of the eyes showed relaxation of the ciliary muscle. This was most noticeable in deep wet shock with atropine cycloplegia.

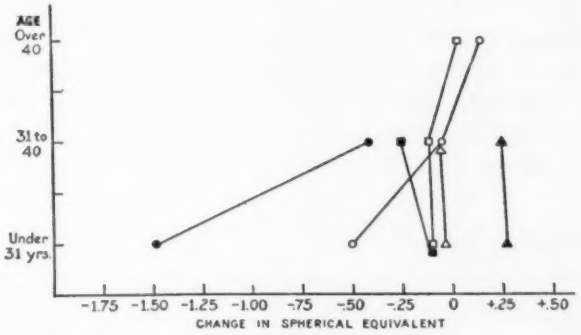

Chart 3.—Graphic presentation of effects on refractive power of age, depth of insulin hypoglycemia and type of mydriasis (table 2).

Changes in deep wet shock during paredrine mydriasis are indicated by black areas; during homatropine cycloplegia, by clear areas, and during atropine cycloplegia, by cross-hatched areas.

This relaxation is not great enough to justify its removal entirely from the realm of possible error in examination. The removal of mental stimulation to accommodation during shock may be a factor. Many organs of the body are innervated by both parts of the autonomic nervous system. Does the ciliary body have a dual innervation? It is known that the thoracolumbar sympathetic system is stimulated during insulin hypoglycemia and that there is increased epinephrine in the blood.

The older the patient, the less the refractive power of the eye was increased with paredrine mydriasis during insulin hypoglycemia. This does not necessarily mean less stimulation of the ciliary muscle in patients of the older groups but may indicate that the ciliary muscle is less able to produce a change in refractive power, owing to decreased elasticity of the lens in older patients.

The results obtained by retinoscopic examination do not always agree with the results obtained by subjective examination, but the results of repeated retinoscopic examinations agree rather closely if the examining distance is kept constant. The change in the youngest group during deep insulin hypoglycemia is so striking with paredrine mydriasis and, when compared with the change with atropine cycloplegia, so different that it exceeds the error inherent in this type of examination.

The fact that the refractive change which occurs during insulin hypoglycemia can be abolished by atropine cycloplegia indicates that it is due to stimulation of the parasympathetic nervous system, which innervates the ciliary muscle. This observation is in agreement with other signs of stimulation of the parasympathetic system, namely, pinpoint pupil, slow heart rate, salivation and increased gastric secretion and motility.

The findings in this study support the observation of an irritable condition of the ciliary muscle during insulin hypoglycemia, as described by Poos. Schmidt's statement that there is no change in refraction during insulin hypoglycemia is essentially true if atropine is used as a cycloplegic. He did not describe his technic.

SUMMARY

Retinoscopic examinations were made on patients receiving insulin hypoglycemia treatment for schizophrenia and other psychoses. Paredrine hydrobromide ophthalmic, homatropine hydrobromide and atropine sulfate were used to dilate the pupils. Examinations were made before and during the hypoglycemia reaction. Definite stimulation of the ciliary muscle was found in some eyes when paredrine was used as a mydriatic. This was most pronounced in the youngest group of patients and was greatest during deep insulin hypoglycemia. Homatropine partially abolished the stimulation of the ciliary muscle during insulin hypoglycemia, and atropine almost completely abolished it, especially during deep insulin hypoglycemia. One patient had so strong a stimulation of the sphincter of the iris during the treatment that his pupils could not be dilated with paredrine, but they could be dilated at other times with paredrine and could be dilated with homatropine during treatment.

CONCLUSIONS

During insulin hypoglycemia there is in some subjects a definite stimulation of the ciliary muscle through the parasympathetic nervous system. This is most evident in young patients and during deep insulin hypoglycemia. Homatropine partially abolishes, and atropine almost completely abolishes, this stimulation.

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FRACTURES OF THE ORBITAL FLOOR

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In this paper I shall describe a not infrequently neglected deformity, present typical case reports of the condition in its various degrees of extent, evaluate the various methods of treatment which have been advocated and describe in detail the treatment which has proved most satisfactory in a group of 34 patients.

Lukens[1], reviewing the literature forty years ago, found 78 cases of traumatic enophthalmos and some nineteen hypotheses to explain its mechanism. Among the etiologic factors suggested were: (1) indirect fracture of the orbital walls, (2) direct fracture of the orbital walls, (3) injury to Muller's orbital muscle, (4) injury to the check ligaments, (5) rupture of Tenon's capsule, (6) atrophy of orbital tissue due to injury of the sympathetic or trigeminal nerves, (7) hemorrhage of the ophthalmic artery behind the ciliary body, (8) minute hemorrhages in the nerve sheaths, particularly of the sympathetic nerves, (9) cicatricial contraction of orbital tissue following inflammation, (10) cicatricial adhesions of the eyeball, (11) cicatricial contraction of the extraocular muscles, (12) absorption of orbital fat due to the pressure incident to severe cellulitis, (13) similar pressure atrophy following orbital hematoma and (14) gross destruction of the orbital contents. Dislocation of the trochlea has also been postulated.[2]

With the passage of time, and particularly with improvement in roentgenographic technic, it is now felt by most observers that of the factors enumerated only the direct and indirect fractures of the orbital wall are significant and that the other factors play little, if any, part

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Submitted as candidate's thesis in partial fulfillment of requirements for membership in the American Ophthalmological Society, 1947.

From the Institute of Ophthalmology of the Presbyterian Hospital, and the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons.

1. Lukens, C.: Traumatic Enophthalmos: Report of a Case, Ophthalmology **3**:30, 1907.

2. Benedict, W. L., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 330.

in producing the condition known as traumatic enophthalmos. Nevertheless, depressed fractures of the orbital floor are not infrequently overlooked, even when associated with more obvious depressions in the orbital rim. Particularly has this been true of severe injuries or war wounds in which the patient's condition is so critical that little attention is paid to what at the moment is of secondary importance. The residua of such injuries may later assume considerable importance, from the standpoint either of ocular dysfunction or of cosmetic appearance.

It has previously[3] been noted that the loss of an eyeball, by enucleation, when associated with a depressed fracture of the orbital floor, may lead to considerable difficulty in the satisfactory fitting of an ocular prosthesis. If the pathologic and mechanical problems are understood, logical measures can be taken to solve them. Usually the same principles will apply whether the fracture is of the orbital floor alone or whether there is an associated displacement of the orbital margin.

All the patients seen in this study had sustained injury several weeks to several months prior to my first observing them. Therefore the late treatment of such fractures is emphasized. For the sake of completeness, however, a review of the literature was undertaken to determine what measures have been used, and are currently in vogue, for the immediate treatment of fractures of the orbital floor and rim.

EARLY TREATMENT OF ORBITAL FRACTURES

Since the emergency treatment of such conditions will rarely fall to the ophthalmologist, most reports are those of general, oral, plastic or rhinologic surgeons.

In 1901 Le Fort,[4] after some forty experiments on cadavers, defined three main lines of weakness through the facial bones along which fractures were most likely to occur (fig. 1). He applied blows of different degrees of violence to various parts of the face and by careful dissection noted the course of fracture lines. An unexpected degree of violence was required to produce a fracture.

1. The simplest fracture divided the maxilla above the alveolar processes, crossed the wall of the nose and the canine fossa, passed beneath the zygoma to the pterygomaxillary fissure and at times divided the pterygoid processes.

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3. DeVoe, A. G.: Experiences with the Surgery of the Anophthalmic Orbit, Am. J. Ophth. **28**:1346, 1945.

4. Le Fort, R.: Experimental Studies upon Fractures of the Upper Part of the Face, Rev. de chir. **23**:208-227, 360-379 and 479-507, 1901; abstracted, Brit. Dent. J. **71**:85, 1941.

2. Severer injury produced a fracture at a higher level, starting at the nasal bones and crossing the nasal processes of the maxilla and the inner wall and floor of the orbit to the region of the infraorbital canal. It then cut off the zygomatic process of the maxilla from the zygomatic bone, continuing backward to the pterygomaxillary fissure.

3. Increased violence produced a third type of fracture, in which the entire face was separated from the cranium. The fracture line crossed the nasal bones, the nasal process of the maxilla and the upper part of the inner wall of the orbit, opening the ethmoid cells nearly to the optic foramen. Near the posterior part of the *sphenomaxillary* fissure

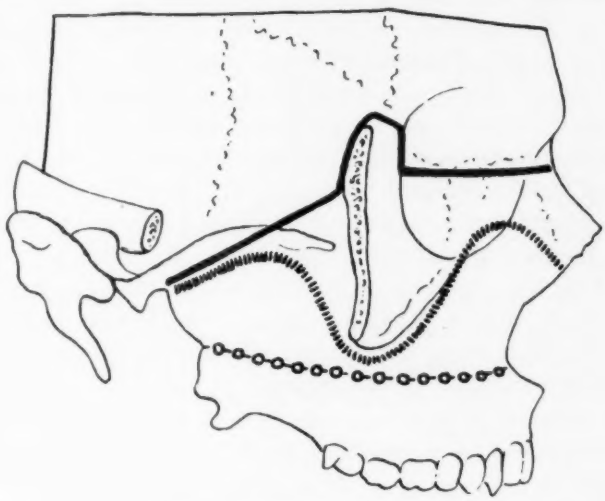


Fig. 1.—Fracture lines of Le Fort.

the fracture line bifurcated, the front arm of the fracture crossing in the outer wall of the orbit to separate the zygoma from the frontal bone, while the posterior arm separated the pterygoid process near its base.

James and Fickling,[5] noting the investigation of Le Fort, went on to point out that the construction of the facial bones was such that a considerable resistance to injury was developed. This, they suggested, was due to the arrangement of areas of density in various bones, as at the orbital rim, and to the curves, buttresses and tie bars exemplified by the zygomatic arch, the pterygoid process and the palatine bone. A blow to the face is transmitted through these structures in a variety of directions and is dispersed so that no great force is directed to the cranium

5. James, W. W., and Fickling, B. W.: The Structure of the Bones of the Face in Relationship to Fracture and Other Aspects of Facial Injuries, Proc. Roy. Soc. Med. **34**:205, 1941.

and its enclosed vital centers. Firm and resistant structures lie on a light framework surrounding the nasal cavity and accessory sinuses. This complex is then attached to the base of the skull so as to absorb an applied force without transmitting it to the skull. The cushioning effect of the easily telescoped nasal-antral-ethmoidal structures will absorb much of a directly applied force. Furthermore, the localized increase in bone density around the teeth and eyes prevents damage to these structures. McIndoe[6] commented on the frequency with which the eye is left uninjured after a severe blow to the orbital region. Typically, lateral force applied to the zygomaticomaxillary area falls on the side of the cheek and is transmitted obliquely inward toward the cranial base. The amount of telescoping and impaction which occurs determines the degree of orbital deformity which follows. McIndoe stated that when moderate force only is applied the usual sites of clinical fracture will be found at the attachments of the frontosphenoidal, orbital and maxillary processes of the zygoma. The maxillary line of weakness is outward and downward through the infraorbital canal and the zygomaticomaxillary junction and backward along the floor of the orbit via the sphenomaxillary fissure. When severe violence is applied to this region, comminution of the zygoma occurs, with impaction into the antrum. A wide separation occurs at the frontomaxillary line of suture, and comminution of the thin orbital floor with prolapse of the orbital content into the antrum occurs.

It should be emphasized that the injuries described in the preceding paragraph are of the type due to a direct blow, such as are more commonly encountered in civilian life, the chief of which are a blow from a fist and injuries incurred in automobile accidents in which the face is thrown against the steering wheel, dashboard or windshield. Many military injuries, on the other hand, are due to explosive fragments and high velocity projectiles, which produce severe local destruction, in addition to expending their force along the lines of weakness previously detailed.

Many patients with orbital fractures, particularly those who have been in severe accidents, have multiple wounds, which may either obscure the orbital injury completely or reduce it to a position of minor importance, pending application of life-saving measures. Nevertheless, a certain proportion of persons so injured are in condition to withstand reduction of the orbital fracture. Most authors agree as to the desirability of this procedure, if possible, pointing out the not inconsiderable cosmetic blemish which may not be obvious until local swelling dis-

6. McIndoe, A. H.: Diagnosis and Treatment of Injuries of the Middle Third of the Face, Brit. Dent. J. **71**:235, 1941.

appears. Some feel that there is less likelihood of diplopia if reduction is rapidly accomplished.

Fractures which are most obvious, such as those involving the zygomatic arch and orbital rim, have often been repaired, and numerous reports are available. Although there is complete agreement concerning the desirability of early treatment, there is no such unanimity concerning the method by which this should be accomplished. Roberts[7] cited Duverney, in 1751, as being the first to mention fracture of the zygoma. Reduction was accomplished by pressure from within the mouth by fingers, a method which others have not found so successful[8] and which Lehmann[9] stated was impossible because of interference from the temporal muscle.

In 1897 Weir submitted 2 case reports[10] in which he described successful results following the elevation of fragments by an approach through the canine fossa into the antrum. This method, either with or without entry into the antrum, has been found satisfactory by a number of surgeons,[11] although the possibility of thus introducing infection has been mentioned by others.[12] In this connection, the point has been raised by a number of workers[13] that since injury to the antrum is present in all these cases, usually to be followed by hemorrhage and infection, treatment properly lies in the domain of the rhinologist. Entrance into the antrum and refracture of the depressed floor, followed by packing of the antrum, has also been suggested as a proper approach

7. Roberts, S. E.: Fracture of the Malar Zygomatic Arch, Ann. Otol., Rhin. & Laryng. **37**:826, 1928.

8. Fracture of the Zygoma, Report from Charing Cross Hospital, Lancet **1**:186, 1872.

9. Lehmann, J. C.: Depression Fracture of the Zygomatic Arch, Zentralbl. f. Chir. **51**:2016, 1924; abstracted, J.A.M.A. **83**:1629 (Nov. 15) 1924.

10. Weir, R. F.: On the Replacement of a Depressed Fracture of the Malar Bone, M. Rec. **51**:335, 1897.

11. *(a)* Garner, J. R.: An Operation for Reducing Depressed Fractures of the Malar Bone and the Zygomatic Arch, Internat. J. Surg. **38**:411, 1925. *(b)* Evans, S. S.: Fractures About the Orbit, South. M. J. **26**:548, 1933. *(c)* Naftzger, J. B.: Fractures of the Nasal Bones Involving the Nasal Accessory Sinuses, Ann. Otol., Rhin. & Laryng. **37**:486, 1928. *(d)* Johnson, M. R.: Depressed Fracture of the Orbital Rim, S. Clin. North America **24**:340, 1940. *(e)* Lothrop, H. A.: Fractures of the Superior Maxillary Bone Caused by Direct Blows over the Malar Bone, Boston M. & S. J. **154**:8, 1906. *(f)* Goldthwaite, R. H.: Plastic Repair of Depressed Fractures of the Lower Orbital Rim, J.A.M.A. **82**:628 (Feb. 23) 1924. *(g)* Eckhoff, N. L.: Injuries of the Face, Guy's Hosp. Gaz. **54**:300, 1940.

12. *(a)* Lothrop.[11e] *(b)* Manwaring, J. G. R.: Replacing Depressed Fractures of the Malar Bone, J.A.M.A. **60**:278 (Jan. 25) 1913. *(c)* Gill, W. D.: Fractures About the Orbit, South. M. J. **21**:527, 1928.

13. Evans.[11b] Naftzger.[11c] Shea, J. J.: The Management of Fractures Involving the Paranasal Sinuses, J.A.M.A. **96**:418 (Feb. 7) 1931.

to the late treatment of fracture of the orbital floor,[14] but Gill[15] stated that it is best to resist the temptation to effect such a reduction and to be content with cosmetic improvement with cartilage and fascial implants. Spaeth[16] expressed agreement with this statement. In 1896 Matas[17] described a method of reducing fractures of the zygomatic arch, although he made no mention of existing deformities of the eye. This procedure consisted simply in passing a large curved Hagedorn needle threaded with silver wire behind the fragment and applying traction. Williams[18] made a similar report. Numerous other reports followed.[19]

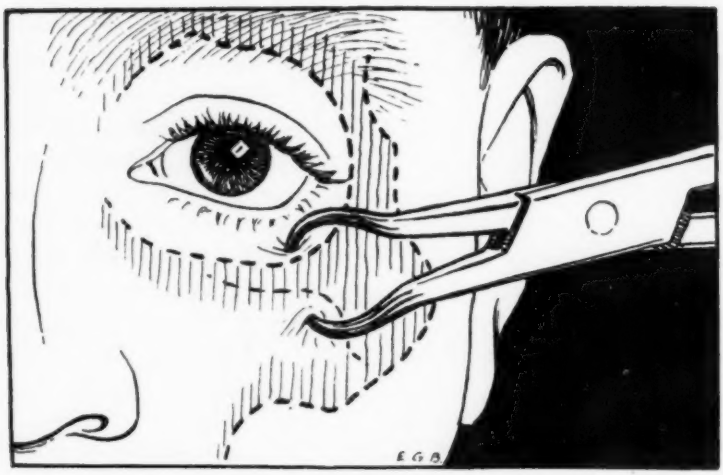


Fig. 2.—Elevation of the orbital rim, with forceps.

Open operation and reduction of the fragments have been described by some authors[20] and viewed with disfavor by others.[21] Manwaring,[12b]

14. Manual of Standard Practice of Plastic and Maxillofacial Surgery, Division of Medical Sciences, Committee on Surgery, National Research Council, Philadelphia, W. B. Saunders Company, 1942, p. 220.

15. Gill, W. D.: Fractures Involving the Orbit, M. World **56**:663, 1938.

16. Spaeth, E. B.: The Immediate and Late Treatment of Injuries About the Orbit, Surg., Gynec. & Obst. **72**:453, 1941.

17. Matas, R.: Fracture of the Zygomatic Arch, New Orleans M. & S. J. **49**:139, 1896.

18. Williams, S. B.: Fracture of the Zygoma, U. S. Nav. M. Bull. **5**:341, 1911.

19. *(a)* McCurdy, S. L.: Depressed Fracture of the Malar Bone, with Report of Three Cases, New York M. J. **76**:849, 1902. *(b)* Ellis, J. A.: Fracture of the Zygomatic Arch, Philadelphia M. J. **3**:467, 1899. *(c)* Gibson, C. L.: Fracture of the Zygoma, Ann. Surg. **55**:457, 1912. *(d)* Footnote 8. *(e)* Lehmann.[9] *(f)* Lothrop.[11e] *(g)* Goldthwaite.[11f] *(h)* Manwaring.[12b] *(i)* Codman, E. A.: Depressed Fracture of the Malar Bone, Boston M. & S. J. **162**:532, 1910.

20. Ellis.[19b] Lehmann.[9] Law, T. B.: A Method of Dealing with Fractures Through the Infraorbital Margin, M. J. Australia **1**:666, 1941.

21. Codman.[19i] Manwaring.[12b]

using the ordinary "cow horn" forceps of the dentist, placed one point of the instrument over the orbital ridge and the other just under the margin of the body of the bone at its outer side. With a little pressure, the skin was penetrated and the bone grasped with any desired firmness. Disengagement and elevation of the bone were easily secured; and since there was no external wound no dressing was needed. Codman[19i] described an essentially similar procedure, as did Gill[22] and Kazanjian.[23] These methods were applicable primarily to fractures involving a large piece of bone at the orbital margin. If a sizable portion of the orbital floor was attached, it was likely to be elevated with the rim. Usually such injuries produced no oculomotor disturbance (fig. 2).

McCurdy,[19a] by screwing a coat hook into the fragment of bone, secured its elevation by traction. A more refined, corkscrew type of surgical instrument was utilized by Roberts.[7] Fixation of the parts after reduction has been effected does not appear to be necessary in the ordinary case, since there are no large muscle attachments to pull them out of place.

Simple fracture of the zygomatic arch or combined fracture of the arch and a portion of the inferolateral wall of the orbit may be most simply repaired by the method of Gillies, Kilner and Stone.[24] After a temporal incision in the hair line has been made, a periosteal elevator is then passed downward beneath the zygoma, and, with the use of the skull as a fulcrum leverage is exerted to raise the bony fragment into position. Subsequent fixation is not necessary (fig. 3).

By any of these methods reduction of simple malar fractures is considered relatively simple. Little orbital deformity is present except at the rim, and there should be little or no displacement of orbital content with attendant ocular malfunction. Combined malar-maxillary fractures, such as were commoner in war injuries, are, however, another matter. Here, some type of splinting is required to retain comminuted fragments in place and to reelevate the orbital floor to its normal position. McIndoe stated that in cases of such fracture it is necessary to enter the antrum by a buccal approach and to elevate the fragments with gauze packing (fig. 4).

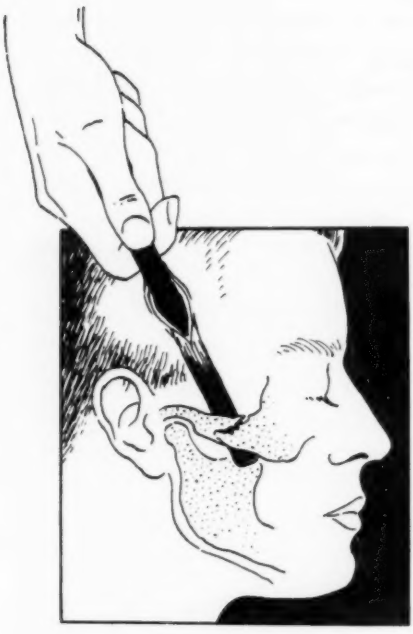
Matthews[25] described the procedure in some detail, entering the antrum through the upper buccal sulcus, above the premolar and the

22. Gill, W. D.: Fractures Involving the Orbit and Paransal Sinuses, with Special Reference to Diagnosis and Treatment, Texas State J. Med. **27**:351, 1931; footnote 12*c*.

23. Kazanjian, V. K.: Treatment of Injuries of the Upper Part of the Face, J. Am. Dent. A. **14**:1607, 1927.

24. Gillies, H.: Kilner, T. P., and Stone, D.: Fractures of the Malar-Zygomatic Compound, with a Description of the New X-Ray Position, Brit. J. Surg. **14**:651, 1927.

25. Matthews, D. N.: The Surgery of Repair: Injuries and Burns, Blackwell Scientific Publications, London, Oxford University Press, 1943, p. 57.



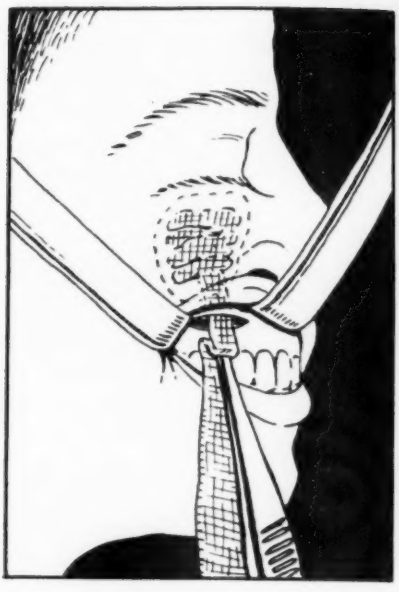


Fig. 3.—Temporal approach for fracture of the zygoma.

Fig. 4.—Buccal approach for fracture of the orbital floor.

first molar teeth. After the lower part of the anterior antral wall is resected, a lever is inserted and impaction of the fractured bone is relieved. The antrum is then packed firmly until the orbital defect is slightly overcorrected. This is considered to be a simple procedure if performed within ten days after the original injury but is considerably more difficult later. The pack is allowed to remain in place for two weeks before its removal, which must usually be done with the patient under general anesthesia. An intranasal antrostomy is performed at the same time in order to allow closure of the buccal wound and to safeguard against later antral infection. Johnson [11d] accomplished the antral packing by the insertion of a water-filled rubber balloon, which he allowed to remain in place for three weeks.

It is admitted that even immediate reduction by the aforedescribed methods is not a guarantee against diplopia.

After fixation of the bony fragments in malunion, which may occur in several weeks, reduction is not usually considered possible. Replacement measures are then necessary. McIndoe stated that, in his experience, it is rare for diplopia to be overcome by subperiosteal insertion of bone or cartilage in the orbit.

Although most authors have stressed the importance of immediate treatment, Straith,[26] in a discussion of the management of facial injuries caused by motor accidents, warned against too hurried procedures of heroic nature. He stated that it is far wiser to delay than to attempt an emergency operation on a patient in poor condition, and in the presence of improper facilities. Serious hemorrhage is considered the only indication for immediate operation. A warning is also sounded to the effect that any serious facial injury should be treated as a potential fracture of the skull until proved otherwise.

The ophthalmologist is more likely to be called for consultation in late treatment of such cases than immediately. Frequently, diplopia is masked by edema of the lids and orbit and does not become annoying for several weeks after the injury. Again, intracranial damage may be so severe that immediate repair work must be postponed while life-saving measures are instituted. Such was the situation with the patients seen in the present series. All had been injured from several months to several years prior to my first seeing them.

LATE TREATMENT OF ORBITAL FRACTURES

Fracture of the orbital floor was recognized in 34 patients and an arbitrary division made into three groups: (1) patients with normal vision in the involved eye, (2) patients with the eye present but with defective vision and (3) patients in whom the eye had been removed.

GROUP 1.—It is surprising how few symptoms may follow a fracture of the orbital floor. The patient may even be totally unaware of any deformity. Not infrequently, the patient has had an initial diplopia, which in the course of a few weeks or months may have disappeared. With a red glass, however, double vision can usually be elicited in some of the extreme positions of gaze. The remarkable compensatory power of the machanism for binocular fusion has been noted by other observers,[27] particularly with relation to slowly progressive exophthalmos.

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26. Straith, C. L.: Management of Facial Inpuries Caused by Motor Accidents, J.A.M.A. **108:**101 (Jan. 9) 1937; Automobile Injuries, ibid. **109:**940 (Sept. 18) 1937.

(Footnotes continued on next page)

This power was again evident in the 6 patients seen in the present series who had a sudden displacement of the globe, experienced immediate double vision but were then able, in the course of a few months, to readjust their binocular vision so that they again saw singly. These patients were well adjusted, able to carry on their usual activities and completely uninterested in further treatment.

CASE 1.—A man aged 22 fell from a moving train and sustained a compound, comminuted, depressed fracture in the right frontal area associated with incomplete paralysis of the third and fourth nerves on the same side. On recovering consciousness after debridement of the craniocerebral wound, he immediately complained of double vision. This steadily became less troublesome and six months after the injury was limited to the upward field of gaze (figs. 5 and 6).

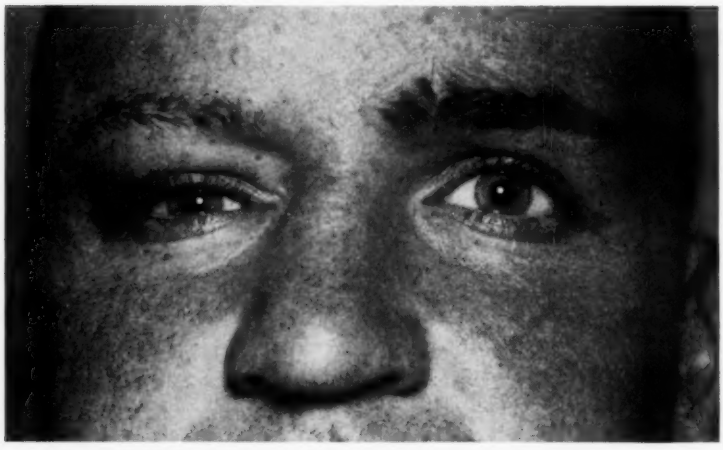

Fig. 5 (case 1).—Appearance following orbital fracture.

The right palpebral fissure measured 7 mm. and the left 9 mm.; vision was 20/15 in each eye, and the exophthalmometer reading was 14 mm. for the right eye and 16 mm. for the left. Roentgenograms showed a depression of the orbital floor into the antrum unattended by injury to the infraorbital rim. A defect in the supraorbital ridge

27. Eagleton, W. P.: Exophthalmos from Surgical Diseases, Especially as to Involvement of the Protective Retrobulbar Space, Arch. Ophth. **14**:1 (July) 1935. Lancaster, W. B.: Fifty Years' Experience in Ocular Motility, Am. J. Ophth. **24**:492, 1941.

was associated with a fracture of the vault and the root of the orbit (fig. 7). Measurements of muscular function revealed weakness of both elevator muscles of the right

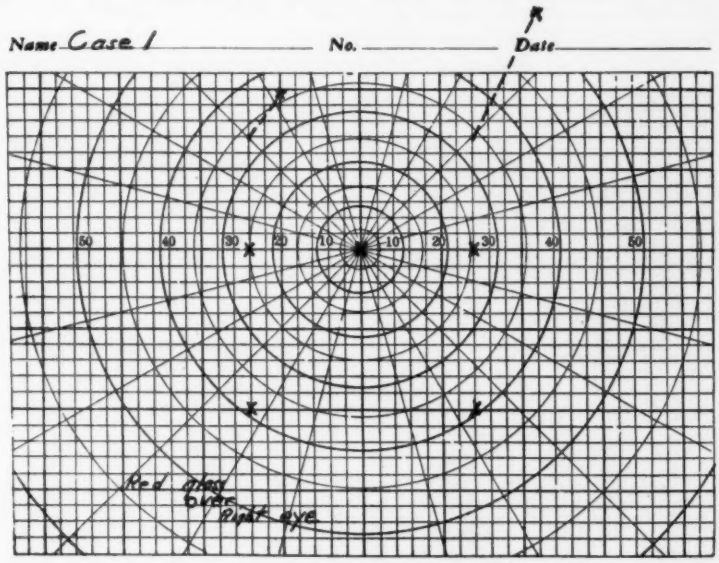

Fig. 6 (case 1).—Plotting for diplopia, with red glass over the right eye.

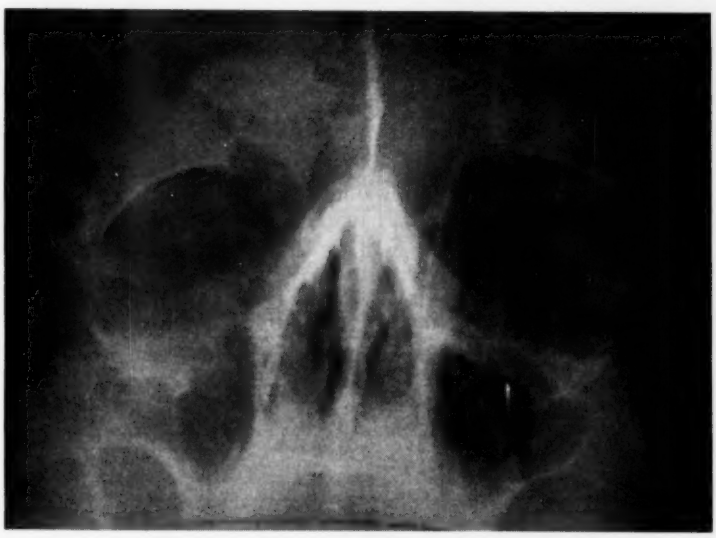

Fig. 7 (case 1).—Roentgenographic appearance of the orbits.

eye, particularly in the field of the superior rectus. When pressure was applied to the globe externally so as to raise it mechanically to its normal position, diplopia appeared

in all positions of gaze. Since diplopia was otherwise present spontaneously only in the upper fields, and not in the horizontal or the lower field, the patient was observed for an additional several months, during the course of which his symptoms became even less noticeable. Surgical intervention was not advised.

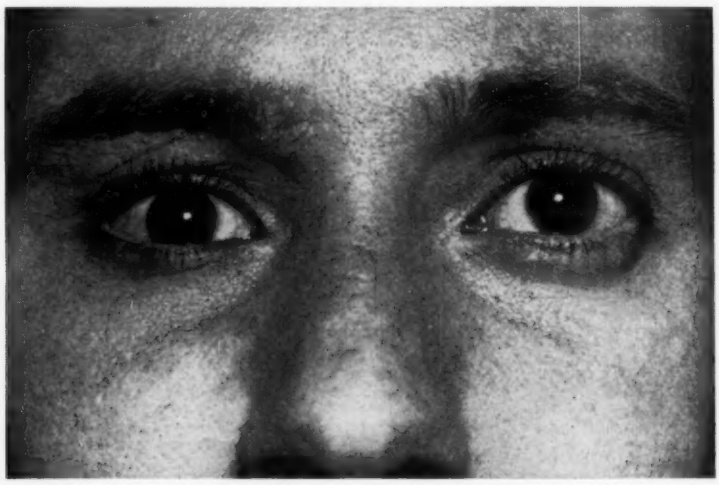

Fig. 8 (case 2).—Appearance following orbital fracture.

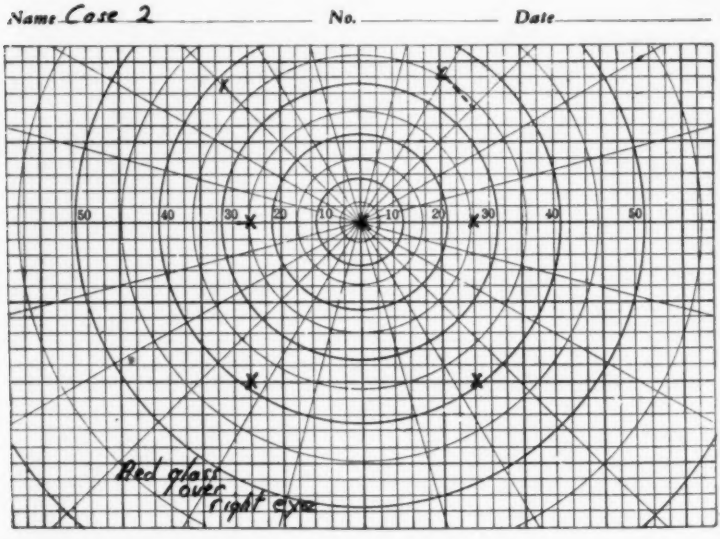

Fig. 9 (case 2).—Plotting for diplopia, with red glass over the right eye.

CASE 2.—While loading bombs in an airplane, the patient, aged 20, was grazed by a falling 500 pound (250 Kg) bomb, which knocked his head forward into another bomb. He received a deep laceration of the right brow, mild concussion and a linear fracture of the skull (fig. 8).

As soon as the dressing was removed from the eye, the patient manifested severe diplopia on looking more than 30 degrees to the right or to the left. The double vision gradually subsided, so that six months later it was not disabling and was present only in his looking up to the extreme right or far down to the right (fig. 9).

A slight palpable deformity was present in the supraorbital ridge. The right eye was 8 mm. lower than the left and was somewhat enophthalmic. Vision was 20/15 in each eye, and examination otherwise revealed no abnormality except for anesthesia of the gums and teeth over the distribution of the right anterior and middle superior dental nerves. Stereoscopic roentgenograms of the orbit revealed well defined fracture of the floor of the orbit, unassociated with deformity of the orbital margin (fig. 10).

Although it was felt that a cosmetic improvement could be obtained by surgical intervention, the patient became practically free from symptoms in the succeeding few months and did not desire further treatment.

Fig. 10 (case 2).—Roentgenographic appearance of the orbits.

REMAINING CASES.—The 4 other patients in this group were seen at intervals varying from two months to three years after the original injury. One of the patients was aware of double vision immediately after injury but two months later noted difficulty only in the extreme portions of the lower fields, and his diplopia was improving so rapidly that no surgical treatment was contemplated. Another patient, three months after injury, had no complaints, although diplopia could be elicited with a red glass in the extreme portions of the upper fields. The third patient, seven months after injury, noted double vision only on looking to the extreme left, and had learned to compensate for this by turning his head to avoid the offending field. The fourth patient, seen three years after the original injury, had never been aware of double vision. All 4 men had objective signs of enophthalmos and roentgenographic evidence of a depressed fracture of the orbital floor.

Comment—Persons with good vision who have sustained this deformity and who have successfully readjusted their ocular muscular balance so that diplopia is absent or present only in the extremes of the unused fields need no further treatment. It is possible that reelevation

of the globe to its normal position would again produce diplopia, for which the patient might or might not be able again to compensate. Although not encountered in this series, cases exist in which severe fracture occurs, depression of the globe follows and the resultant diplopia is of a degree that renders spontaneous recovery impossible.[28] In such cases the logical treatment would seem to be an operative procedure which would elevate the globe to a more nearly physiologic position, so that the normally strong mechanism for binocular fusion would be in a position to take over. Such a case, in which the defect was repaired by subperiosteal insertion of bone from the iliac crest, was described by Converse.[29] Two weeks after operation the diplopia was said to have disappeared in all fields except in extreme upward gaze. Detailed ophthalmologic data were not given. Givner[30] also recently described notable improvement in a case in which repair was effected with preserved cartilage. Diplopia was not specifically mentioned, although strong hypotropia persisted and was thought to be due to injury of the inferior oblique muscle. Vision was 20/20 in each eye.

It is of some interest to note that in 1915 Murphy[31] replaced the outer wall of an orbit with an osteoperiosteal graft from the tibia so effectively that the eye was thereby "fully elevated to its former level." Previous attempts to elevate the eyeball by injection of paraffin had been notably unsuccessful.

GROUP 2.—Eight patients, presenting varying degrees of deformity in association with fractures of the orbital floor, were found to have suffered severe loss of visual function. Since a blow severe enough to produce a large depression in the orbital floor will usually be sufficient to produce considerable intraocular damage as well, most patients with severe fracture will fall into this group or into group 3. Since the cosmetic appearance may be poor, many of these patients are anxious to have the globe replaced to as nearly normal anatomic position as possible. This correction is not always easy. The lines of fracture are usually united to the periorbita by scar tissue, and attempts to separate the tissue may either perforate the periorbita and allow herniation of orbital fat or penetrate the antral mucosa and so open an avenue of

28. Ungley, H. G. and Suggit, S. C.: Fractures of the Zygomatic Tripod, Brit. J. Surg. **32**:287, 1944.

29. Converse, J. M.: Two Plastic Operations for Repair of Orbit Following Severe Trauma and Extensive Comminuted Fracture, Arch. Ophth. **31**:323 (April) 1944.

30. Givner, I.: Reconstruction of the Floor of the Orbit, Am. J. Ophth. **29**:1010, 1946.

31. Old Compound Fracture of the Right Malar Bone Resulting in Loss of the External Wall of the Orbit, in Murphy, J. B.: Surgical Clinics, Philadelphia, W. B. Saunders Company, 1915, vol. 4, p. 125.

infection. I believe that herniation of the orbital fat is undesirable because of the ease with which its nutrition is impeded. Such interference may, in turn, cause atrophy of the fat, lessen the orbital volume and so add to the already existing defect. Perforation of the antral mucosa may or may not be harmful. In the majority of cases there is little, if any, infection in the antrum, and prompt healing by scar and callus formation will occur. Once the adhesions have been separated, it has been found easy to elevate the globe to a proper horizontal position. To effect the necessary forward protrusion is, however, not always simple. Particularly is this so in patients who have a concomitant dehiscence in the roof of the orbit. In these patients, insertion of material in the orbital floor is satisfactory up to a certain point, beyond which addition of more material does not cause further advancement of the globe but apparently displaces the orbital contents superiorly into the anterior cranial fossa.

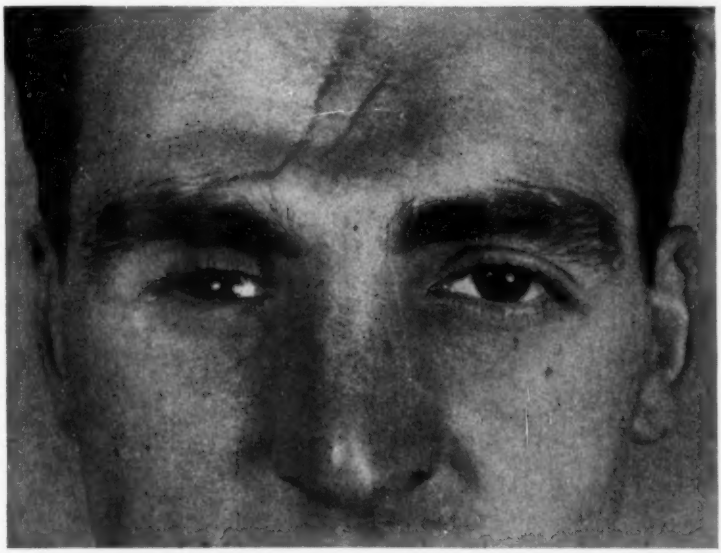

Fig. 11 (case 3).—Preoperative appearance.

CASE 3.—The patient, aged 20, incurred a severe compound, comminuted, depressed fracture of both frontal and temporal bones when struck by fragments of a mortar shell. On recovery from his critical condition, and after having obtained a plastic repair of the deformity of the skull, the patient was anxious to secure a cosmetic improvement of the disfiguring enophthalmos incident to a depressed fracture of the orbital floor (figs. 11 and 12). His condition was further complicated by the presence of a large hole in the roof of the orbit, allowing communication with the anterior cranial fossa. Traumatic chorioretinitis had reduced vision in the involved eye to 15/400 with correction. Accordingly, about seven months after his original injury, the floor of the orbit was exposed, the depressed fracture identified and preserved cartilage placed sub-

periosteally over the injured region. This subsequently was found to produce an undercorrection, so that six weeks later the region was again exposed and tantalum ribbon packed posteriorly above the previously placed cartilage. Beyond a certain point, addition of more ribbon failed to produce protrusion of the globe and, in fact, caused retraction. This was thought to be due to the dehiscence in the orbital roof and the probability that the orbital content was herniating into the anterior cranial fossa. Although the patient's condition is somewhat improved, the postoperative result is not considered successful (fig. 13).

Fig. 12 (case 3).—Roentgenographic appearance of the orbits.

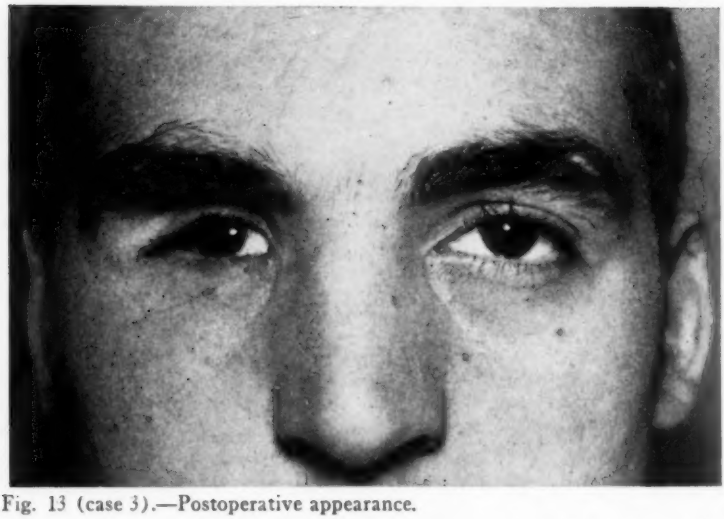

Fig. 13 (case 3).—Postoperative appearance.

CASE 4.—A man aged 28 was injured by a rifle bullet, which entered above the right malar region and lodged in the parieto-occipital area. On regaining consciousness one week later, he became aware of a homonymous field defect, the result of injury to the occipital lobe, as well as reduction of vision to 4/400 in the right eye, due to traumatic chorioretinitis. Two day after his injury an operation was performed, using the

Fig. 14 (case 4).—Preoperative appearance.

Fig. 15 (case 4).—Roentgenographic appearance of the orbits.

approach through the canine fossa, and the anterior walls of the maxillary sinus were exposed. The upper third of the anterior wall and the lateral third of the infraorbital ridge were observed to be fractured. The sinus was filled with old blood, fragments of bone and orbital contents, which had prolapsed laterally into the cavity. These fragments were removed, and a large intranasal opening was made into the inferior meatus. The postoperative course was uncomplicated. Examination two months after the orig-

inal injury (fig. 14) revealed a palpable defect in the infraorbital ridge, depression of the right globe about 3 mm., divergence 14 degrees of arc and enophthalmos of 4 mm. Stereoscopic roentgenograms confirmed the depression of the orbital floor (fig. 15).

In order to secure a cosmetic improvement, therefore, the floor was exposed and the periosteum elevated with some difficulty from the comminuted, irregularly healed fracture. Glass wool was inserted until the proper position of the globe had been obtained. The postoperative course was not remarkable and a satisfactory cosmetic result was obtained (fig. 16).

REMAINING CASES.—Of the 6 remaining patients in this group, 1 presented a picture similar to that of patient 3. In addition to a dehiscence in the floor of the orbit, there was a communication between the roof and the anterior cranial fossa. Implantation of preserved cartilage in the floor subperiosteally was successful in elevating the globe to its proper level but did not secure its forward protrusion, 6 mm. of enophthalmos remaining unchanged. Addition of material was suggested, but the patient was satisfied with his cosmetic appearance and desired no further surgical treatment.

Fig. 16 (case 4).—Postoperative appearance.

Two patients with roentgenographic evidence of fracture of the floor did not present sufficient cosmetic blemish to warrant elevation of the floor, although 1 had a disfiguring loss in the inferior orbital rim, which was replaced with preserved cartilage.

The 3 remaining patients were transferred to hospitals closer to their homes after preliminary plastic work on the lids and adjacent structures was accomplished, but before the orbital repair could be carried out.

Comment.—If a severe disfigurement is associated with a depressed fracture of the orbital floor and a nonfunctioning eyeball, it can be materially improved by mechanical elevation of the entire orbital content. In 1 case described, this was accomplished by subperiosteal insertion of preserved cartilage, supplemented with tantalum ribbon; in the other, by a similar use of glass wool. Any inert mass should accomplish the same result. Such procedures have been tolerated with a variety of materials and have not resulted in loss of motility of the eyeball. In

1 case, not included in this series, insertion of autogenous rib cartilage in the presence of preexisting conjunctival edema resulted in a severe orbital cellulitis. This eventually subsided, after systemic administration of penicillin, and the graft was not extruded. The globe, however, became frozen in the socket, and all motility was lost. It is possible, but not certain, that the antrum was entered during the dissection, allowing contamination of the orbital fat. Attention is also called to the additional complication which may arise if the orbital roof is damaged as well as the floor.

GROUP 3.—Twenty patients were observed who had a depressed fracture of the orbital floor associated with the loss of an eyeball. It is particularly easy to overlook such a fracture when the eye has been removed. The sulcus in the upper lid is thought to be one of the unavoidable complications which follow extensive wounds, and since many of these patients had had gunshot wounds it was logical to assume that destruction of orbital tissue had been caused by trauma from the missile. Clinically, the condition should be suggested by observation of a deep socket, either with or without the presence of an implant. All attempts to fit a satisfactory artificial eye, either glass or plastic, be it by use of the injection technic or by the addition of flanges or bolsters to the prosthesis, are doomed to failure. An unsightly loss of the superior orbital fold will persist. Routine roentgenographic examination in cases of this type will demonstrate frequently that the condition is due, at least in part, to an alteration in the orbital floor.

Numerous devices have been tried in an effort to correct this condition. As a rule, they depend on either or both of two principles: (1) use of a delayed orbital implant, such as Wheeler's grooved sphere implant,[32] or (2) subcutaneous insertion of a dermal graft, fascia lata or other material in the region of the depression. The former procedure is automatically sound, since it fills the deficiency in orbital content which has resulted from the enlargement of the orbit attendant on the displacement of the floor. The defect in the procedure is that only a small implant can be inserted as a delayed procedure and be retained. The volume of such an implant is small, rarely over 2 cc., which is insufficient except in the least severe deformities. The second procedure seems to me unsound, since it is not directed at the source of the difficulty. It will, however, improve the defect to a considerable extent.

Insertion of material directly into the orbit, but outside Tenon's capsule, is undesirable because such insertion requires dissection into orbital fat which, as has been previously noted, is suspectible to trauma,

32. Wheeler, J. M.: Colected Papers on Ophthalmic Subjects, New York, Columbia University Press, 1939, p. 427.

with resultant atrophy. The end result of such insertion may then be a cosmetic defect as great as, if not greater than, the original condition. The most logical approach to the problem, then, is the insertion of material into the orbit outside the periorbita. This provides a new floor for the orbit and, by raising its content, automatically obliterates the sulcus in the upper lid. Such a procedure was carried out on 9 of the 20 patients in this group and, in addition, was performed on 6 additional patients who presented the deformity of the upper lid but who did not have fracture of the orbital floor.

CASE 5.—A man aged 24 was struck in the eye by a fragment of shell, receiving a severe laceration of the lid and such damage to the right globe that enucleation was performed. A large metallic foreign body was removed from the region of the greater wing of the right sphenoid bone and a primary repair of the lid performed at the same time. When first seen by me two months later (fig. 17), the patient was observed to

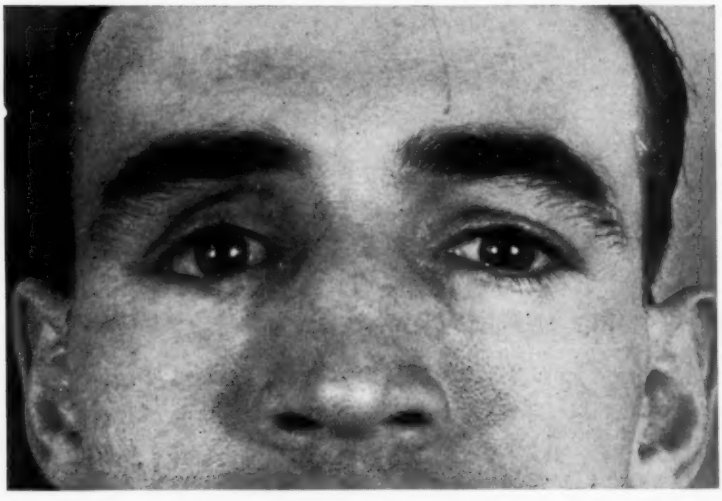

Fig. 17 (case 5).—Preoperative appearance.

have notching of the lid at the site of the injury, shortage of tissue in the lower fornix and a deep socket without implant. Stereoscopic roentgenograms of the orbit revealed an old comminuted fracture of the left zygoma near the maxillozygomatic suture with a depression of the floor of the orbit into the antrum of 2 to 3 mm. (fig. 18).

As a primary procedure, a halving repair of the lower lid was performed and the patient fitted with a plastic artificial eye. Considerable depression of the upper lid was noted to persist. Consequently, about six months after his original injury, preserved cartilage, carved to fit and measuring 7 by 14 by 28 mm., was inserted subperiosteally in the floor of the orbit. With the fitting of another eye, a satisfactory cosmetic appearance was obtained (fig. 19).

CASE 6.—The patient was injured in a forced airplane landing, during which his head was thrown forward onto an instrument. The globe was shortly enucleated and a gold sphere implanted. Healing was uneventful, and careful roentgenographic studies

Fig. 18 (case 5).—Roentgenographic appearance of the orbits.

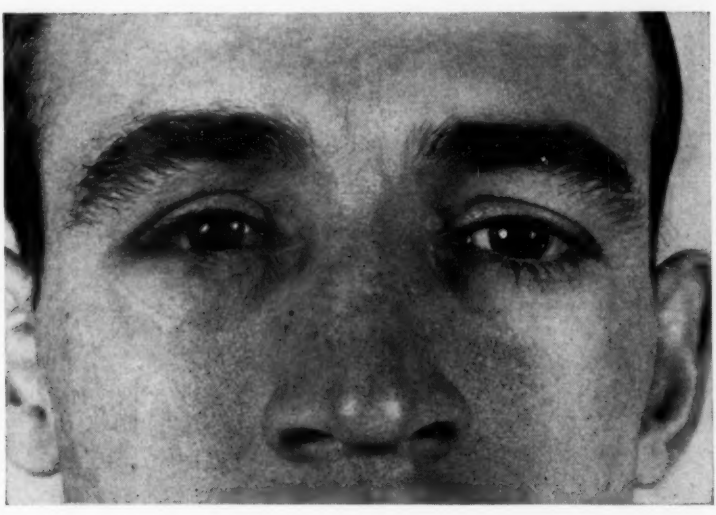

Fig. 19 (case 5).—Postoperative appearance.

were not made. Numerous attempts to fit an artificial eye, both glass and plastic, failed in securing a presentable result. Examination revealed an abnormally deep socket and an implant which could be palpated deep in the lower nasal quadrant. Fracture of the orbital floor was suspected and confirmed roentgenologically (figs. 20 and 21).

About two years after the original injury, preserved cartilage was placed subperiosteally in the floor of the orbit. The site of fracture was demonstrated and observed to be firmly healed by callus. With the fitting of another plastic eye, considerable cosmetic improvement in the enophthmos was obtained, although movement remained poor (fig. 22).

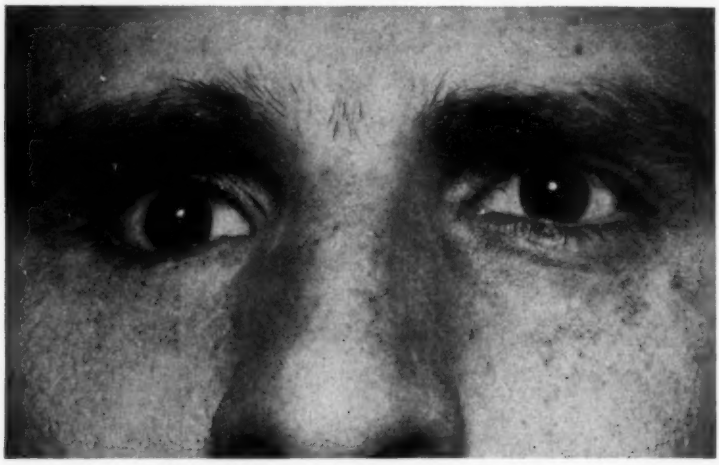

Fig. 20 (case 6).—Preoperative appearance.

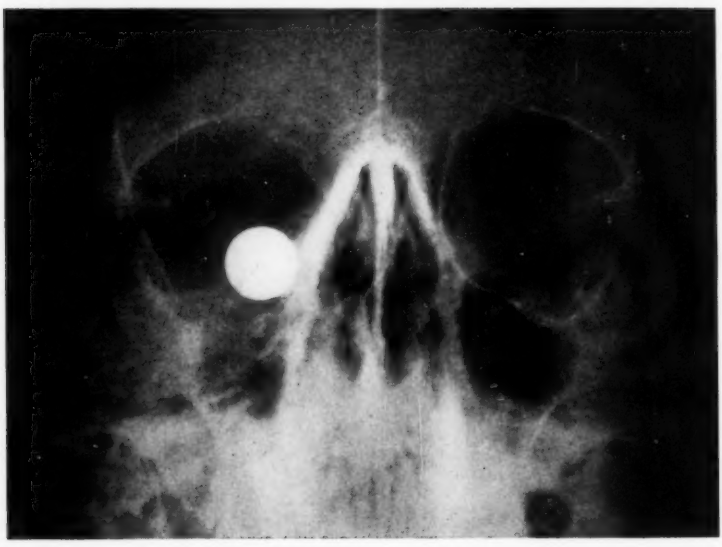

Fig. 21 (case 6).—Roentgenographic appearance of the orbits.

OTHER CASES.—In addition to cases just described with demonstrable fractures of the floor, there exists another, rather large, group of cases in which there develops either early or late, after enucleation, a disfiguring loss of the fold in the upper lid. The mechanism of this occurrence is debatable but may be related to trauma of orbital

tissue during dissection, with subsequent atrophy. The defect may occur with or without the presence of an implant and is not rectifiable by any maneuvers of the maker of the artificial eye. After a trial of various methods to correct the deformity, such as delayed implantation of spheres or acrylic wedges of various shapes, as well as subcutaneous insertion of dermal grafts in the upper lid, it was thought worth while to attempt subperiosteal implantation in the floor. This was done in 6 cases, in 4 of which preserved cartilage was used and in 2 glass wool. The procedure was well tolerated and the immediate result satisfactory. Because of wartime conditions, none of the patients has been followed for more than a year and one half, admittedly too short a time on which to base positive conclusions. It is felt, however, that the procedure is worth further trial.

Comment.—Any unusually deep socket in a case of anophthalmia should be viewed with suspicion and roentgenologic investigation of

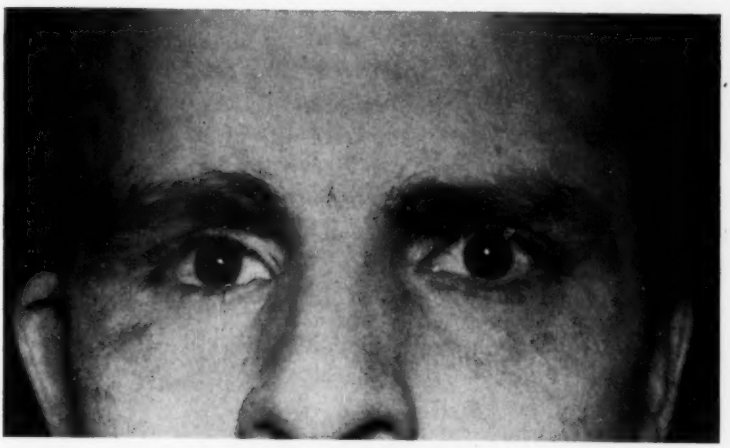

Fig. 22 (case 6).—Postoperative appearance.

the status of the orbital floor undertaken. Particularly should this be done if an implant is present and found to be displaced inferiorly. Attempts at fitting artificial eyes by any technic will be unsuccessful in that apparent enophthalmos and loss of the normal superior orbital fold will persist. Considerable cosmetic appearance can be obtained by the insertion subperiosteally in the floor of the orbit of inert material to increase the orbital volume.

ROENTGENOGRAPHIC TECHNIC

As has previously been intimated, suspicion of the condition must precede its diagnosis. Not infrequently the patient has had routine roentgenograms of the skull. From these it has been impossible to evaluate the condition of the orbital floor. Pfeiffer[33] stated that failure

33. Pfeiffer, R. L.: Traumatic Enophthalmos, Arch. Ophth. **30**:718 (Dec.) 1943.

to detect this condition is more often to be attributed to lack of correct technic than to inexperience or carelessness in interpreting the results. He emphasized the importance of proper centering and positioning so that a symmetric projection is obtained and pointed out that stereoscopic examination is essential. It should be noted that in every case of traumatic enophthalmos examined by Pfeiffer there was roentgenographic evidence of fracture of the orbit. Baltin reported similar observations.[34] Other observers have commented on the lack of reliability of roentgenograms in determining orbital fractures,[35] but in a properly centered stereoscopic projection the two orbits can be compared with considerable detail. All the patients in the present series had stereoscopic roentgenograms taken in both the Caldwell and the Waters position. All had lateral views, and many had roentgenograms of the optic canal as well. In my experience, the Waters position has been most valuable in determining the presence and the extent of the deformity in the orbital floor. Single roentgenograms were of little value, since they frequently yielded a picture hardly distinguishable from that of sinusitis. When seen stereoscopically, however, the downward bulging of the orbital floor into the maxillary sinus has been clearly demonstrable. The degree of prolapse of the orbital content has been said to be greater when the antrum is large. This is logical but was not specifically noted in this series.

Planigraphy has been said by some[36] to yield valuable information concerning various types of orbital fractures, but I have had no experience with this method.

TREATMENT

As previously noted, a number of patients seen late after an injury to the orbital floor will require no treatment because their mechanism for binocular fusion will have adjusted itself to the displacement of the globe, and cosmetic defect will not be great. In a great many others, however, treatment will be imperative.

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34. Baltin, M. M., and Svyadoshch, B. I.: Roentgen Diagnosis of Blunt Injuries and Gunshot Wounds of the Orbit, Vestnik oftal. **17**:786, 1940; **18**:306, 1942; abstracted, Am. J. Ophth. **24**:1338, 1941.

35. Gill, W. D.: Fractures of the Facial Bones, with Special Reference to Involvement of the Paranasal Sinuses and Orbit, South. M. J. **27**:197, 1934. Hoffman, W., and Loepp, W.: Value of Roentgenography in Injuries of the Orbit, Arch. f. Ophth. **134**:82, 1935; abstracted, Am. J. Ophth. **18**:894, 1935.

36. Culler, A. M.: Fractures of the Orbit: The Demonstration of the Orbit by Planigraphy, Tr. Am. Ophth. Soc. **38**:348, 1940. King, E. F., and Samuel, E.: Fractures of the Orbit, ibid. **64**:134, 1944.

Earlier writers[1] expressed the belief that most attempts to overcome diplopia and restore the globe to its proper position would be futile, but recently reports have appeared in the literature demonstrating various methods of approach to the problem. Injection of paraffin was attempted and was soon discarded.[37] To overcome enophthalmos tenotomy of all four rectus muscles was said to be helpful.[38] The use of diathermy, ingestion of potassium iodide and other ineffectual procedures have been described.

In 1941 Lyle[39] presented a group of 7 patients who had been greatly helped by operative procedures on the extraocular muscles. He also noted that most of these patients had been previously told that nothing could be done to correct their condition. At least four months was allowed to elapse between the time of injury and surgical repair. He found that the vertical deviations in this group were due to injury of either the superior rectus or the inferior oblique or of both, and in general, he carried out weakening procedures on the contralateral synergistic muscle. Three patients with hyperphoria of about 2 D. were rendered orthophoric, and 3 others, with deviations of 10 to 20 D., were made practically so. One patient, with a deviation of 45 D., was not helped greatly. All operations were carried out with local anesthesia, without injection of anesthesia into the muscle, and with Maddox rod fixation on an overhead light. The use of prisms in cases of low error was suggested. There seems to be no question that relatively low degrees of error can be corrected if necessary by such methods, particularly when the deviation is due to injury of muscles or nerves rather than to severe displacement in the orbital walls.

The idea of mechanically raising a prolapsed globe to its proper position is not new. As has been noted, it was described by Murphy in 1915, but the statement has been made that cartilage placed immediately above the inferior portion of the prolapsed periorbita fails to produce a satisfactory result.[14] This has not been our experience or that of others.[40] The question also arises whether it is better to use autogenous

37. Darier, A.: Therapeutics, in Pyle, W. L.: An International System of Ophthalmic Practice, Philadelphia, P. Blakiston's Son & Co., 1910, p. 198.

38. Lagrange, F.: Medical and Surgical Monographs, New York, D. Appleton & Company, 1918, vol. 4, p. 802.

39. Lyle, T. K.: Some Cases of Post-Traumatic Diplopia Following Head Injury and Their Treatment, Tr. Ophth. Soc. U. Kingdom **61**:189, 1941.

40. Gill.[15] Spaeth, E. B.: The Principles and Practice of Ophthalmic Surgery, ed. 2, Philadelphia, Lea & Febiger, 1941, p. 73. Figi, F. A.: Traumatic Scarring and Depressed Fracture of the Right Malar Bone and Orbital Border: Cartilage Implant, S. Clin. North America **12**:947, 1932. McIndoe, A. H.: The Treatment of Old Traumatic Bony Lesions of the Face, Surg., Gynec. & Obst. **64**:376, 1937.

or preserved cartilage in such reconstructions. Peer[41] recently reviewed the fate of such grafts and stated the opinion that autogenous grafts in adults continue to live, neither increasing nor decreasing in size, and that such grafts in infants will continue to grow, since cartilage early in life has not lost its growth potential. Webster[42] also expressed the belief that it is better to use autogenous cartilage. In several of the patients included in this series, I had occasion to operate a second time, two to four months after the original operation, either to readjust the position of the cartilage or to add more. On these occasions biopsy specimens were taken of the previously placed grafts, both autogenous and preserved, and subjected to microscopic examination. In none was there evidence of viable cartilage cells, and all showed beginning phagocytosis peripherally. It may well be that, as Peer has suggested, these autogenous grafts were too thick or that the site of their implantation was lacking in the necessary vascularity and that diced cartilage would be more suitable.[43] Be that as it may, it appears uncertain that any type of cartilage graft will endure permanently when buried subperiosteally in the floor of the orbit.

For this reason, attempts were made to secure some easily obtained and well tolerated material. Cancellous bone from the crest of the ilium has been recommended, but its use presents added difficulties to the procedure. The use of fascial and dermal grafts offers the same objection as cartilage. Acrylic wedges and plates[44] and inert metals, such as tantalum and "vitallium," have been used, but there is the objection to their employment that they must be largely performed to the anticipated size of the defect and are not easily adjusted on the operating table. In the present state of knowledge, acrylics are not tolerated by all human beings, although it is probable that new methods of curing and preparation will shortly correct this. Tantalum also has the disadvantage of developing high temperatures by induction, and should the patient subsequently receive diathermy he might be badly burned. In 1 case in this series, however, tantalum ribbon was used without complication.

It was felt that the ideal material for filling orbital defects would be some form of wool or packing. Recent reports concerning the use of

41. Peer, L. A.: Cartilage Grafting, S. Clin. North America **24**:404, 1944.

42. Webster, J. P.: Some Procedures for the Correction of Ear Deformities, Tr. Am. Soc. Plastic & Reconstruct. Surg. **13**:123, 1944.

43. Peer, L. A.: Diced Cartilage Grafts: New Method for Repair of Skull Defects, Mastoid Fistula and Other Deformities, Arch. Otolaryng. **38**:167 (Aug.) 1943.

44. Souders, B. F.: Elevation of Orbital Contents with Plastic Plates, Crile General Hospital Military Ophthalmological Meeting Procedures, November 1945, p. 28. Sherman, A. E.: Choice of Procedure in Ophthalmic Plastic Surgery, ibid., November 1945, p. 121.

glass wool as suture material[45] suggested its use in the orbit. To date, it has been used in 4 of the cases reported in this series and has been well tolerated. In 1 other case, seen elsewhere, the material was inserted subcutaneously to build up an orbital rim. A sterile accumulation of serum developed immediately after operation but has subsided over a period of several months. Whether the material will warrant further use remains to be seen. It is, however, easily handled and inserted into the irregular crevices frequently found in a depressed fracture of the orbital floor.

OPERATIVE TECHNIC

An incision, 15 to 20 mm., is made in the crease of the lid centrally over the inferior orbital rim and the dissection carried down through the orbicularis to the orbital rim about 5 mm. below its margin. With a knife, the periosteum is incised and its elevation with periosteal elevators begun. The periosteum will be found firmly adherent at sites of fracture and along the orbital fissures but can usually be dissected free nearly to the orbital apex. As much packing is then inserted into the orbit as is necessary to produce the proper position of the globe and fulness of the upper lid. The periosteum is then tightly closed with fine nylon (000000); the edges of the skin are approximated and a pressure dressing is applied. If an artificial eye is worn, it is put in place before application of the dressing. The only postoperative complication which has been encountered to date is anesthesia over the distribution of the zygomatic nerve for several weeks, presumably due to the stretching of that nerve in the orbit during the elevation of the periosteum. External deformity is negligible, although when a large amount of material has been inserted temporally there is a tendency for the outer canthus to be raised. In some fractures, particularly those with coexisting separation of the zygomaticofrontal synchondrosis, this is an asset rather than a defect. It is believed desirable not to perforate the periorbita and allow the orbital content to herniate because of the ease with which such tissue is devitalized. Entry into the antrum will also eventually occur, but since in these old injuries there is little inflammatory residue, orbital cellulitis is unlikely to develop and prompt healing with scar tissue will occur. As a rule, postoperative reaction is minimal, and the dressings can be removed within a week. If, months or weeks later, it becomes apparent that insufficient correction has been accomplished, there is no contraindication to repetition of the procedure.

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45. Scholz, R. P., and Mountjoy, P. S.: Fiberglas Suture Material: Preliminary Report, Am. J. Surg. **55**:619, 1942.

SUMMARY

Thirty-four cases of fracture of the orbital floor were observed and the following conclusions drawn.

1. The immediate care of such fractures will rarely be an ophthalmologic problem because of the multiplicity of the injuries, often of a vital nature, which usually accompany the condition. A review of the literature has been made to determine the measures most frequently used in immediate treatment.

2. When weeks or months have elapsed since the original injury, the ophthalmologist is the one best fitted to carry out reparative work.

3. Such repair may take the form of operation on the extraocular muscles or may require substitution of inert material in the orbital floor in order to restore orbital volume or elevate the globe to a proper position.

4. In anophthalmic patients the cosmetic appearance can often be improved by restoration of the orbital floor.

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DEVELOPMENT OF CHANGES IN VISUAL FIELDS ASSOCIATED WITH GLAUCOMA

ADOLPH POSNER, M.D.
AND
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NEW YORK

IT IS GENERALLY admitted that a comparative study of the visual field is the most important index of the progress of the disease in a given case of glaucoma. Since there is considerable variation in the evolution of the field defects in individual cases, it was deemed advisable to undertake a survey and classification of a large sample of unselected cases. The material for the present study consists of approximately 2,000 visual fields representing 350 patients with glaucoma from private practice.[1]

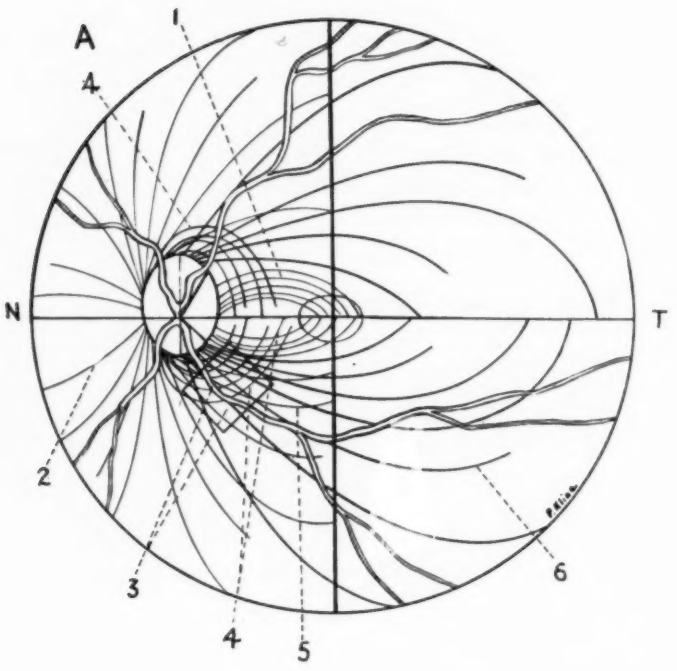
By appropriate grouping of these fields, it was found possible to follow the evolution of the various components of the field defect. An attempt was then made to formulate a hypothesis which would adequately explain the pathogenesis of the elements of the glaucoma field. These field studies have been carried out by a uniform method over the past fourteen years. The technic will be described later.

Figure 1*A* is a schematic representation of our concept of the relation of nerve fibers to one another and to the vascular tree. From the diagram, it is readily seen that the papillomacular bundle occupies two thirds or more of the temporal half of the optic nerve. All the fibers derived from the temporal half of the retina (nasal field) are crowded into the remaining upper and lower sixths of the temporal half of the nerve. The fibers coming from the nasal half of the retina (temporal field) occupy the nasal half of the optic disk.

In lesions of the optic pathways, the dividing line between the nasal and the temporal field is a vertical line drawn through the fixation point. We believe with Evans[2] that the vertical line through the macula divides the temporal from the nasal portion of retina. We have, therefore, drawn

1. Part of the material used in this study was taken from the files of the late Dr. Mark J. Schoenberg.

2. Evans, J. N.: Classic Characteristics of Defects of the Visual Field, Arch. Ophth. **22**:410-431 (Sept.) 1939.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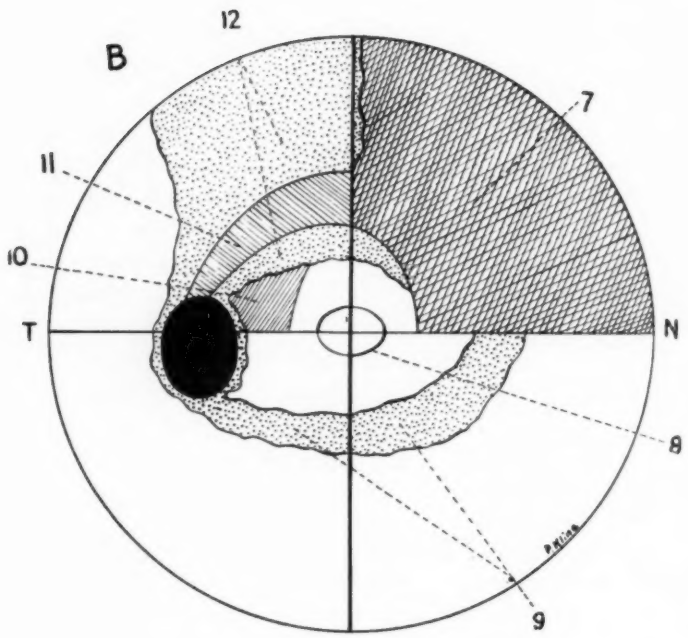
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all the fibers which supply the peripheral portion of the retina nasal to the vertical meridian as belonging to the nasal half of the nerve. In this respect, our diagram is at variance with those generally found in textbooks, in which the area included between the macula and the optic disk is not accounted for.

The foregoing assumption is supported to some extent by the work of Brouwer and Zeeman.[3] These authors made an incision in the lower part of the retina between the macula and the optic disk. They found some degeneration in the area of the crossed peripheral fibers in the optic tract and the external geniculate body. Traquair[4] admitted that the segregation of crossed and uncrossed fibers into separate bundles holds true in the optic nerve even "immediately behind the eye," and he assumed that this "would necessitate a rearrangement of fibers between the retina and the beginning of the nerve." We know of no anatomic proof of this rearrangement. We thus feel justified in assuming that the area of the retina included between the vertical meridians passing through the fovea and the optic disk, respectively, is nasal retina. The nerve fibers derived from this area enter the nasal half of the nerve.

The relation of the circulation to glaucoma has been stressed by numerous authorities. More recently, Reese and McGavic[5] have demonstrated that a connection exists between the blood pressure and the changes in the fields in cases of glaucoma. Evans[6] described capillary aneurysms associated with glaucoma, which may be related to a derangement in the capillary sphincter mechanism. Although the entire retina is probably affected by glaucoma, the areas of greatest vulnerability appear

3. Brouwer, B., and Zeeman, W.P.C.: Projection of Retina in Primary Optic Neuron in Monkeys, Brain **49**:1-35 (March) 1926.

4. Traquair, H. M.: Introduction to Clinical Perimetry, ed. 5, London, Henry Kimpton, 1946, p. 75.

5. Reese, A. B., and McGavic, J.: Relation of Field Contraction to Blood Pressure in Chronic Primary Glaucoma, Arch. Ophth. **27**:845-850 (May) 1942.

6. Evans, J. N.: The Capillary Sphincter in the Human Retina, Arch. Ophth. **37**:182-188 (Feb.) 1947.

Fig. 1.—Schematic representation of the evolution of defects in the visual fields associated with glaucoma. *A* indicates arrangement of nerve fibers and blood vessels in the retina; *B* shows a typical visual field in glaucoma. *1* is papillomacular bundle; *2*, nasal fan; *3*, area of greatest nutritional disturbance; *4*, nasal fibers to area between disk and macula; *5*, nasal fibers; *6*, temporal fibers; *7*, defect in upper nasal field, showing nasal step; *8*, fixation area; *9*, lower arcuate scotoma; *10*, juxtacecal step; *11*, upper arcuate scotoma; *12*, intermediate zone between arcuate scotoma and nasal defect.

The area of maximum circulatory disturbance (*3*) corresponds in part to the arcuate scotoma (*11*). Nasal and temporal fibers passing through this area may become involved, resulting in the juxtacecal step (*10*) and nasal defects (*7*), respectively. Intermediate zone (*12*) is partly neural and partly circulatory in origin.

to be in the proximity of the superior and inferior temporal branches of the central retinal vessels. This may be accounted for by the great crowding of nerve fibers in this region. All the temporal fibers, in addition to many nasal fibers, of necessity pass through this narrow zone (fig. 1*A*, 3). It is possible that the perimacular area drains, partially at least, into this region of the retina, thus increasing still further the strain on the circulation. The area around the inferior temporal vessels appears to be more vulnerable than that adjoining the superior temporal vessels, for reasons which will be given later.

Figure 1*B* shows schematically the changes in the fields associated with glaucoma. The earliest change is an accentuation of the angioscotoma tree.[7] These scotomas are first reversible, or at any rate show fluctuations on repeated examinations. Later, however, the permanent arcuate scotoma is formed. This probably represents local damage to the cellular and synaptic structures of the internal layers of the retina. It is reasonable to assume that the nerve fibers passing through this area are also eventually affected. Interruption of the nerve fibers is manifested by a field defect at an area remote from the point of involvement and corresponds to the distribution of the end organs of these fibers. If a few scattered fibers are thus affected, there will result a depression of the upper nasal field to the smallest stimulus. As more fibers become involved, the defect takes on the appearance of a nasal step. The latter, when developed, ends with a steep slope (in the sense of Traquair's terminology) along the horizontal meridian, in contrast with the arcuate scotoma, which is characterized by a more gradual slope. We shall attempt to show in the field studies to follow that, generally speaking, a steep slope indicates a neural origin, whereas a gradual slope denotes that the scotoma is chiefly of circulatory origin.

Although the majority of nerve fibers which pass through the area of greatest vulnerability come from the temporal portion of the retina, a certain number of nasal nerve fibers also transverse this region. Among the latter are fibers which supply the area between the disk and the macula (fig. 1*A*, *4*). Judging from the low visual acuity of this region, these fibers are probably few. Since they supply the retina beneath the papillomacular bundle, it is easily understood that they may not be detected by red-free ophthalmoscopic examination, by which the more superficial layers are visualized. Involvement of these fibers produces a scotoma such as that in figure 1*B*, *10*. This defect is frequently found in the fields in cases of glaucoma, and examples will be shown later. A similar configuration in various stages of development was noted in

7. Evans, J. N.: An Introduction to Clinical Scotometry, New Haven, Conn., Yale University Press, 1938, p. 104.

studies of the visual fields reported by several authorities.[8] These authors did not differentiate this area from the rest of the arcuate scotoma and apparently regarded it as an integral part of the latter. The neural origin of this scotoma is evidenced by the fact that it ends abruptly at the horizontal meridian; in this respect, it is analogous to the nasal step of Rönne. For the sake of brevity, this scotoma will be referred to as the juxtacecal step.

DEVELOPMENT OF THE ARCUATE SCOTOMA

In glaucoma, the earliest changes detected in the region corresponding to the arcuate scotoma consist in widening and accentuation of the angioscotomas. Figure 2*A*, right eye, is the field of a patient with recurrent glaucomatocyclitic crises in that eye.[9] The angioscotomas widened during the attack but became normal after subsidence of the ocular hypertension. The left eye was amblyopic.

B and *C* of figure 2 show fields from cases of early glaucoma. Repeated examinations showed persistent widening of the angioscotoma tree, although the pattern varied from time to time.

Figure 3*A*, right eye, shows a more advanced stage, with a permanent widening of the upper angioscotoma. The left eye shows the end result of this process, consisting in a merging of the angioscotoma with the corresponding nasal field defect to form a nasal step.

Figure 3*B*, left eye, shows the arcuate defect in a shape characteristic of Bjerrum's scotoma. It arches upward and nasally above the fixation area to end in the horizontal meridian. It is permanent, having remained unchanged for several years. The terminal segment of this scotoma has a steep slope and is probably caused by damage to the nerve fibers which pass through the region of impaired circulation in the retina. The proximal segment has a gradual slope and is chiefly of circulatory origin.

Figure 3*C*, right eye, shows a relatively dense defect in the nasal field, from which a tongue-shaped projection extends toward the upper angioscotoma. This scotoma is reminiscent of the description of the formation of the arcuate scotoma, as given by Traquair,[10] namely, that it begins at some distance from the blindspot and extends toward it. It is seen from

8. van der Hoeve, J.: Visual Field Defects and Operative Procedures in Glaucoma [table 9, fig. 11], Ztschr. f. Augenh. **34**:277-289, 1915. Traquair,[4] p. 126, fig. 71*B*, 73*A* (left eye), fig. 78*A* (right eye). Elliot, R. H.: A Treatise on Glaucoma, ed. 2, New York, Paul B. Hoeber, 1922, p. 251, fig. 64 (right eye) and fig. 65 (left eye). Bjerrum, J.: An Additional Method of Visual Field Measurements and the Visual Field in Glaucoma [fig. 16], Verhandl. d. Internat. M. Cong. **4**:78, 1890.

9. Posner, A., and Schlossman, A.: A Syndrome of Recurrent Attacks of Unilateral Glaucoma with Cyclitis Symptoms, Arch. Ophth. **39**:517 (April) 1948.

10. Traquair,[4] p. 134.

the figure that the entire area which corresponds to the upper angioscotoma tree is functionally depressed, but that this depression is most pronounced in two zones. The one near the blindspot corresponds to the

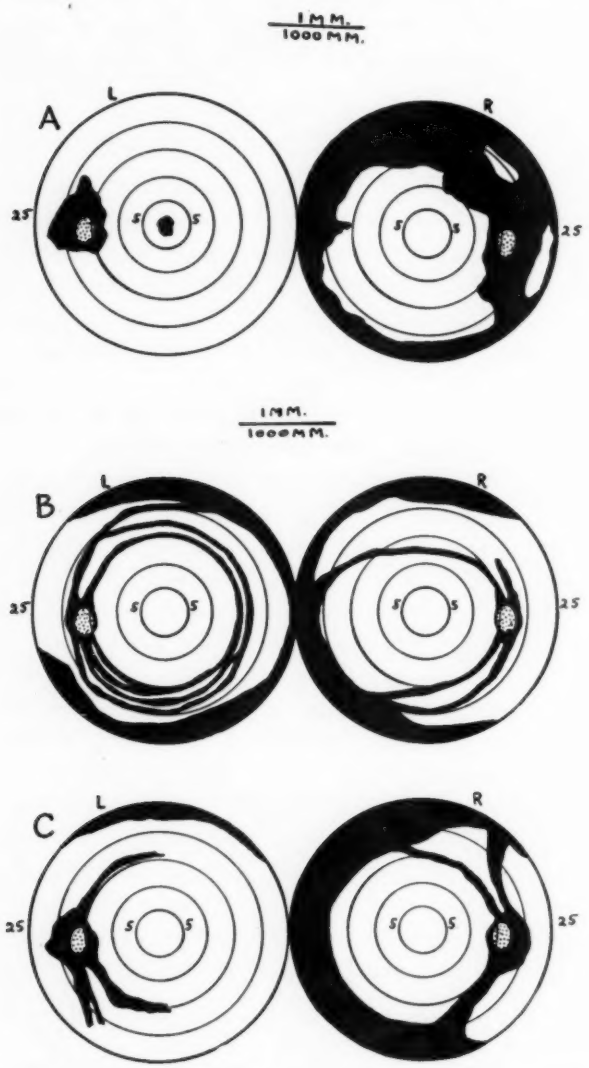

Fig. 2.—(*A*) Right eye: widened angioscotomas, which are reversible (recurrent glaucomatocyclitic crises in the right eye. (*B* and *C*) Widened angioscotomas, variable pattern, in a case of early glaucoma.

greatest circulatory disturbance; the zone extending from the nasal defect has a neural element added to the circulatory element common to the entire area.

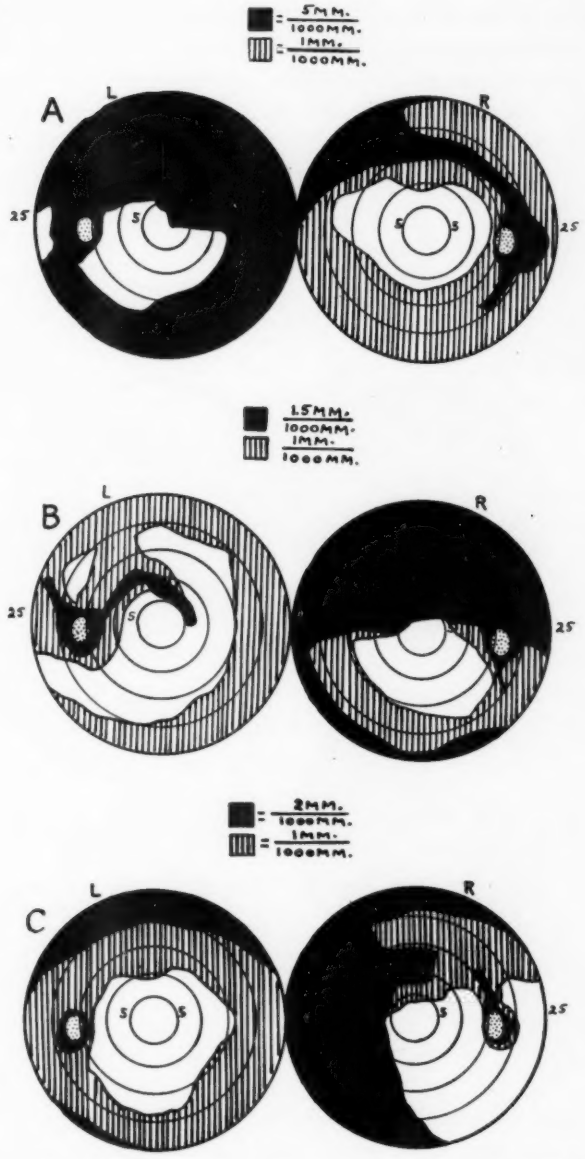

Fig. 3.—(*A*) Right eye: early arcuate scotoma, permanent; left eye: upper nasal defect merging with arcuate scotoma. (*B*) Right eye: early upper horizontal hemianopsia; left eye: arcuate scotoma with nasal step. (*C*) Right eye: nasal defect with incomplete arcuate scotoma of circulatory and neural origin; left eye: moderate generalized contraction.

The field of the right eye shown in figure 4*A* may be explained by assuming that a bundle of nerve fibers belonging to the nasal portion of the retina is damaged as it crosses the area of maximally impaired nutrition. This is substantiated by the fact that the arcuate scotoma stops abruptly at the vertical meridian. The dividing line between the circulatory and the neural elements of this scotoma is probably at *a*.

Figure 4*B*, left eye, illustrates the relation of the arcuate scotoma to the defect in the nasal field. The latter ends in a line which corresponds

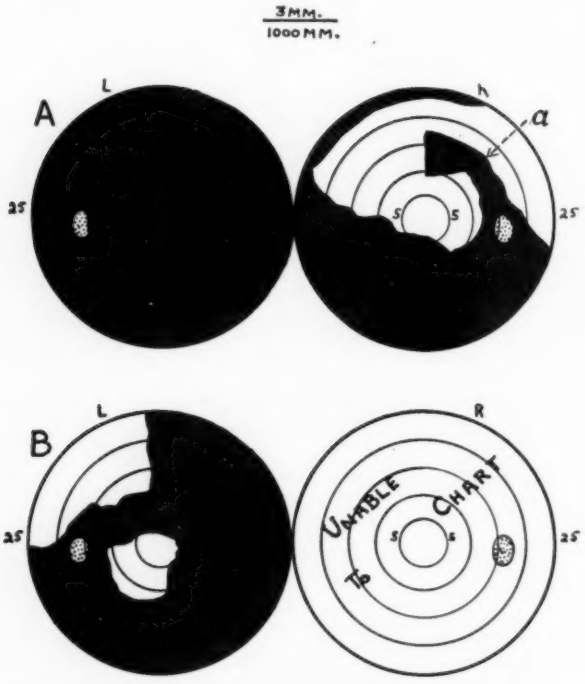

Fig. 4.—(*A*) Right eye: upper arcuate scotoma, ending in vertical meridian; at division between neural and circulatory elements; left eye: blindness. (*B*) Left eye: upper arcuate scotoma with juxtacecal step, connecting with area of nasal hemianopsia.

to the vertical meridian passing through the fixation point, and is thus probably neurogenic. The lower border of the upper arcuate scotoma extends in a straight line along the horizontal meridian as far as 6 degrees from the fixation point. This represents the juxtacecal step.

These eight field studies demonstrate that the arcuate scotoma is composed of neural and circulatory elements, which may be combined in a varying quantitative relation to each other. The involvement of nasal fibers is demonstrated by the juxtacecal step (fig. 4 *B*) and by the abrupt ending of the arcuate scotoma at the vertical meridian (fig. 4 *A*). In-

volvement of the temporal fibers is shown by the nasal step. It will be seen that when two sizes of test objects were used scotomas of the circulatory origin had a more gradual slope than the neurogenic scotomas.

DEVELOPMENT OF THE NASAL FIELD DEFECT

The arcuate scotoma is described as typically ending in the horizontal meridian in a nasal step. A defect involving both the upper and the lower nasal quadrant is assumed to be produced by a combination of two

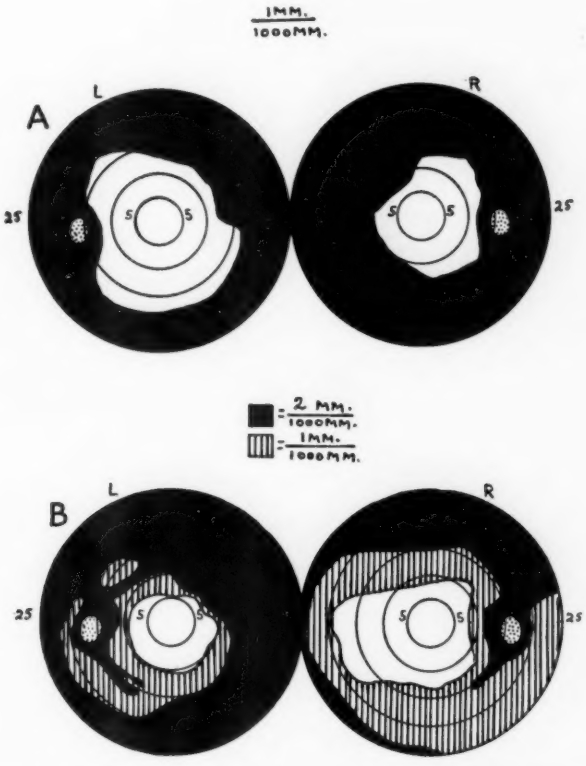

Fig. 5.—(*A*) Early irregular nasal contraction. (*B*) Right eye: early generalized contraction; left eye: generalized contraction, predominantly nasal.

nasal steps. Analysis of many field studies shows that a typical nasal step is by no means a constant finding but that defects in the nasal field may take on various shapes. A few examples are shown in figures 5 to 8.

Figure 5 *A* shows the irregular indentation of the nasal field to a 1 mm. test object in a case of early glaucoma. This change may be partly an expression of the generalized lowering of retinal function, which is more pronounced in the nasal field as a result of impairment of a few

scattered temporal fibers as they cross the zone of maximum nutritional disturbance in the retina. Figure 5 *B*, left eye, shows a similar field, but with more advanced changes.

Figure 6 *A*, left eye, shows two types of early defects in the nasal field. The lower is caused primarily by a confluence of angioscotomas, while the upper exhibits an early nasal step which is probably neural and is not connected with the corresponding angioscotoma. Figure 6 *B*, right eye,

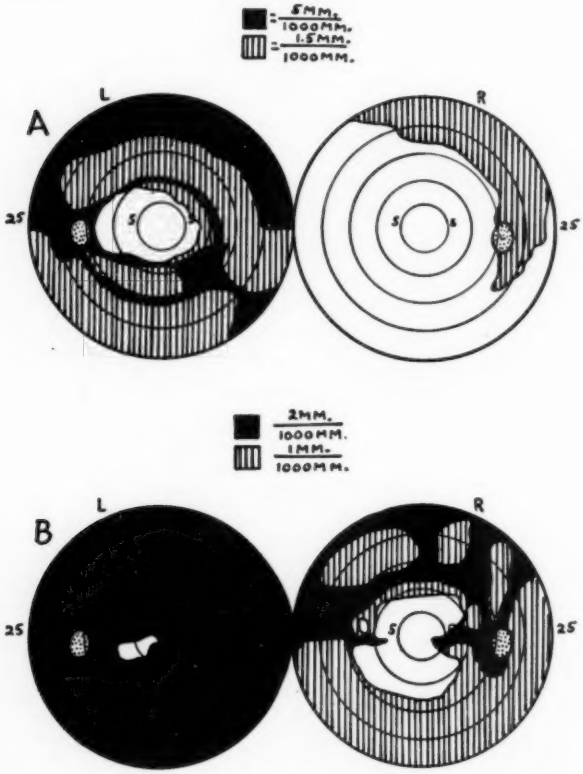

Fig. 6.—(*A*) Right eye: normal; left eye: early upper nasal step (neurogenic), lower nasal defect (of circulatory origin). (*B*) Right eye: upper nasal step, probably of circulatory origin, connected with widened angioscotomas; left eye: late contraction of field.

demonstrates clearly how the confluence of angioscotomas may produce a nasal step and thus simulate a nerve fiber bundle defect. This may be explained by the presence of a vascular raphe in the horizontal meridian.

Figure 7 *A* shows bilateral defects in the nasal field in later stages of development. The right field shows, in addition to the nasal step, generalized contraction to a 1 mm. test object. The left eye, at first glance, appears to show a typical nasal step. However, on careful analysis, it will

be noted that the lower border does not extend to the horizontal meridian passing through the fixation point, but is situated 4 degrees above.

Figure 7 *B*, left eye, demonstrates a typical defect in the upper nasal quadrant, which ends at a steep slope in the horizontal meridian. This is connected with the blindspot by two arcuate scotomas, which lie in an area of depressed retinal function.

Figure 8*A*, left eye, is a similar field, but without a pronounced arcuate defect. Figure 8*B*, right eye, shows in addition to a nasal de-

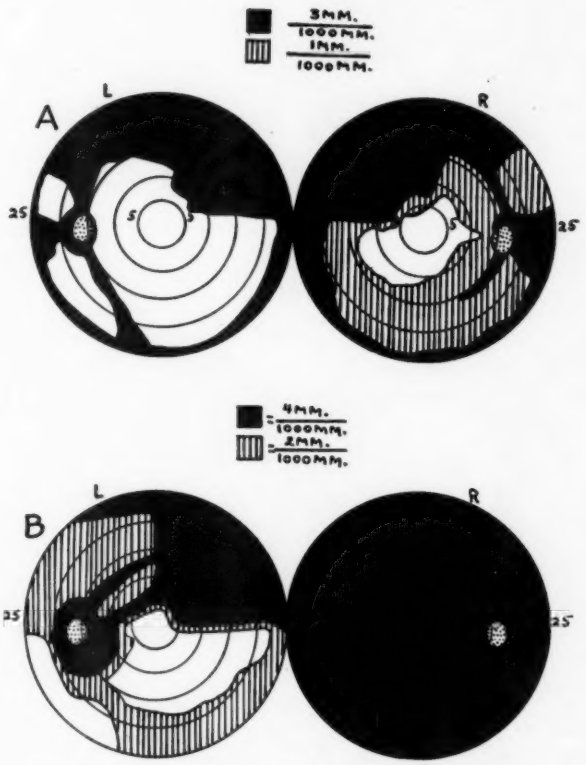

Fig. 7.—(*A*) Bilateral upper nasal defects. (*B*) Right eye: blindness; left eye: defect of upper nasal quadrant (neurogenic), connecting with arcuate scotoma.

fect, moderate encroachment on the upper half of the fixation area and a juxtacecal step which extends from the arcuate scotoma to the horizontal meridian. Figure 8 *C* shows a nasal step in the right eye and loss of both nasal quadrants in the left eye. The latter also demonstrates the juxtacecal step.

Like the arcuate scotoma, the defect in the nasal field contains both circulatory and neural elements. The nasal step is the result of involve-

ment of nerve fibers as they cross the area of maximal circulatory disturbance of the retina. Figure 1 shows why the defect in the nasal quadrant, when present, generally occurs on the side of the more advanced arcuate scotoma.

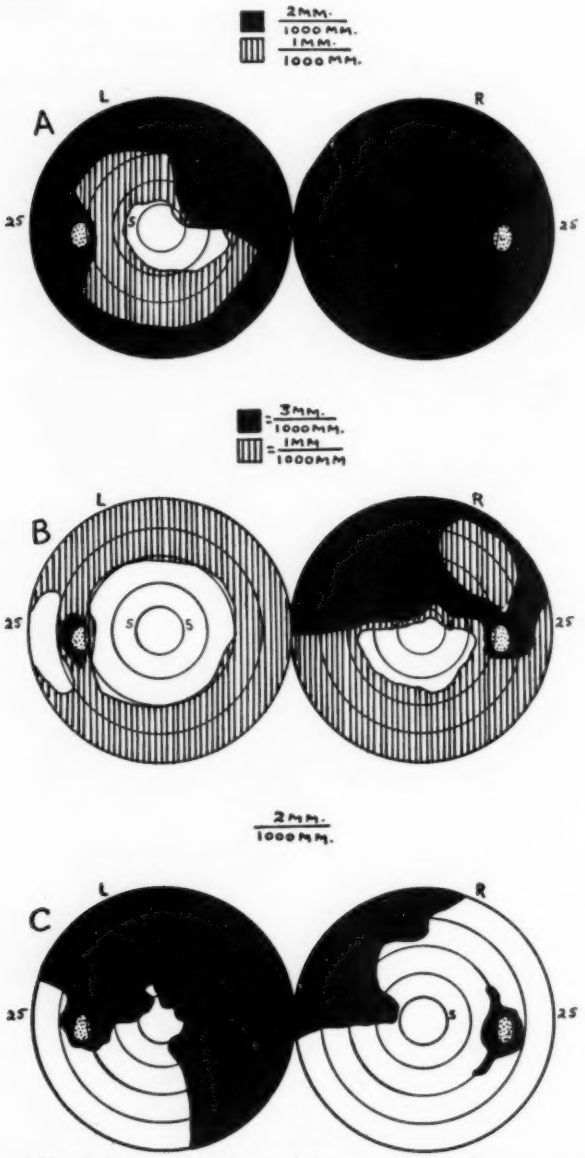

Fig. 8.—(*A*) Right eye: blindness; left eye: defect of upper nasal quadrant. (*B*) Right eye: defect of upper nasal quadrant, with arcuate scotoma and juxtacecal step; left eye: mild generalized contraction. (*C*) Right eye: defect of upper nasal quadrant with nasal step; left eye: nasal contraction, predominantly of upper quadrant, connecting with blindspot and juxtacecal step.

OTHER FIELD DEFECTS

While the arcuate scotoma and the defect in the nasal field belong to the classic picture of the field associated with glaucoma, other types of defects are occasionally encountered. In 3 cases the temporal field alone was affected. In 1 of these cases this defect was related to widening of the lower temporal angioscotoma. In several cases a more or less generalized contraction of the field was an early sign; but here the contraction often appeared to be more advanced in the nasal field (fig. 5).

In the majority of cases the fixation area is spared until late. However, early involvement of this region is not unusual. This may occur either as the result of extensions from the angioscotomas or through direct damage of some of the fibers of the papillomacular bundle which pass in close proximity to the area of greatest nutritional disturbance in the retina. The rectangle in figure 1*A* was drawn to include some of the papillomacular fibers in order to demonstrate how such partial involvement of the fixation area may come about.

TECHNIC USED IN THIS STUDY

The initial study of the field in each case was made on the perimeter and the tangent screen. Subsequent examinations were carried out at varying intervals, more frequently on the tangent screen. The perimeter used was a nonrecording instrument, with a radius of 250 mm. and a built-in illuminating unit giving an illumination of 7½ foot candles.

The tangent screen was 1 meter square, covered with black wool felt and placed 1 meter from the patient. For most of these field studies, illumination was provided by an over-head light which, aided by reflection from a light-colored wall behind, yielded a uniform illumination of 5 to 6 foot candles. For the past ten years, small white spherical test objects, as devised by Evans, were used. They were supplemented by the Berens test objects when sizes larger than 1.5 mm. were necessary.

In addition to the conventional methods of scotometry, the Evans technic of angioscotometry[11] was adapted for use with the tangent screen.

COMMENT

Although the defects in the visual fields associated with glaucoma may assume a wide variety of patterns, they can be broken up into component units which are more or less characteristic of the disease, namely, early widening of the angioscotomas, generalized contraction to small test objects, the arcuate scotoma of Bjerrum, nasal field defects, the nasal step of Rönne and the juxtacecal step. These component parts show a varying

11. Evans,[7] p. 61.

degree of circulatory and neural elements in their pathogenesis. The relative preponderance of one or the other of these elments may be estimated by the slope of the border of the scotoma and by its relation to the distribution of nerve fibers and blood vessels in the retina (fig. 1*A* and *B*). Our concept of the pathogenesis of the field defects associated with glaucoma was outlined in an earlier section of this paper. Two of the more commonly accepted alternative theories are (1) damage to nerve fibers at the margin of the glaucomatous cup, and (2) traction on the nerve fibers, resulting from the receding lamina cribrosa.

It is inconceivable how hydrostatic pressure can push the nerve fibers against the optic cup, since the nerve fibers do not form a membrane impervious to water. On the contrary, they are permeated by intraocular fluid, and hence the hydrostatic pressure around them must necessarily be the same. The physical factors involved in the formation of glaucomatous cupping are different from those affecting the nerve fibers within the eyeball. In the first case, the pressure behind the lamina cribrosa is less than the intraocular pressure, but within the eyeball the hydrostatic pressure is approximately the same throughout. In fact, Traquair[12] stated:

> . . . the frequently advanced explanation of the production of field defects in glaucoma by compression of the nerve fibers against the edge of the scleral foramen cannot be regarded as satisfactory.

Stretching of the nerve fibers by the receding lamina cribrosa may be a factor, but is certainly not an important one. The visual field is not as a rule related to the amount of cupping, though in a few cases it is related to the site of the greater pallor. Furthermore, it is evident from the histologic sections of glaucomatous eyes that, even in deep cups, the nerve fibers are not stretched between the edge and the floor of the cup (like fiddle strings) but follow the contour of the excavation.

In only 3 of 400 cases was there early involvement of the field temporal to the blindspot. The reason for the preponderance of nasal defects is not definitely known. Two factors are suggested as a partial explanation. The majority of nerve fibers which pass through that part of the retina which corresponds to the arcuate scotoma go to the temporal portion of the retina, and their involvement causes a defect in the nasal field. Moreover, reference to figure 1*A* demonstrates the extreme crowding in the region in question. For this reason, the nerve fibers passing through this area would be more vulnerable to circulatory or metabolic dysfunction.

The upper nasal quadrant is more often affected than the lower. Again, carrying this concept a little farther, it will be seen from figure 1 *A* that there is relatively more crowding of those fibers which emerge

12. Traquair,[4] p. 135.

from the lower temporal quadrant of the disk than of those arising from the upper temporal quadrant. This is because the horizontal raphe, which passes through the fovea, intersects the optic disk about 1.5 degrees below its geometric center. This difference is significant when one realizes that the vertical diameter of tbe disk is only about 7 degrees. Additional evidence may be adduced from analysis of the cecocentral scotoma in cases of tobacco amblyopia, strabismus and other conditions.

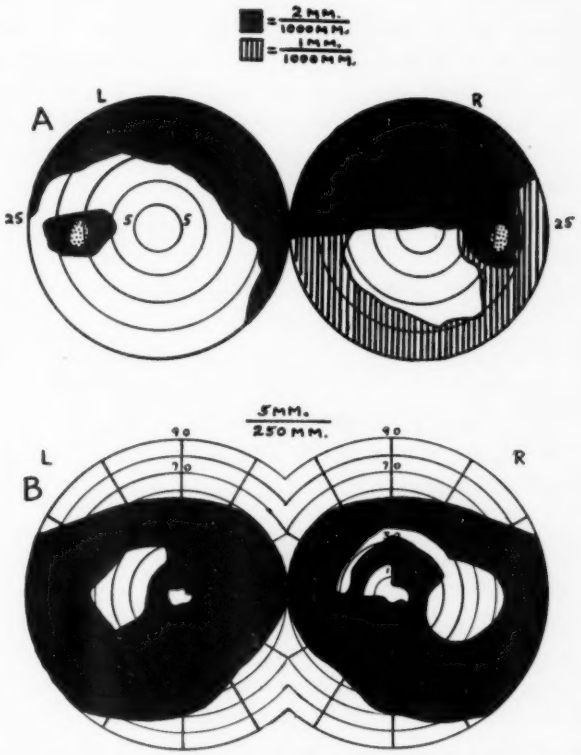

Fig. 9.—(*A*) Right eye: upper horizontal hemianopsia and moderate enlargement of the blindspot; left eye: upper nasal contraction and moderate enlargement of the blindspot. (*B*) Field in a case of late glaucoma, showing preservation of small central and temporal islands.

In the majority of such cases, the cecocentral scotoma extends from the fixation point in a horizontal direction and meets the blindspot above its geometric center. This, again, indicates that the functional division between the upper and lower halves of the optic disk is not identical with the geometric center, but lies below it and is on a level with the horizontal raphe.

Where both nasal quadrants are involved to give the appearance of a nasal hemianopsia, it is not necessary to assume that two nasal steps have joined. A more or less generalized contraction of the field, especially the nasal half, is characteristic of glaucoma. This may be due to a diffuse involvement of nerve fibers originating in the temporal half of the optic nerve. This view is corroborated by fields showing defects of the nasal quadrant which are not delimited by the horizontal raphe. The circulatory elements may also play a role in the formation of this type of defect.

The formation of horizontal hemianopsia (fig. 9*A*) in glaucoma may be interpreted as a fusion of three components, namely, the arcuate scotoma, the juxtacecal step and the nasal step. Encroachment on the fixation area may be due to direct involvement of the papillomacular bundle, or it may be of circulatory origin and related to the arcuate scotoma. The horizontal hemianopsia found in the closure of a temporal branch of the central retinal artery may originate in a manner similar to that just described.

It is well known that the fixation area is usually spared until late in the course of the disease. The reason for this is not definitely known. Figure 1*A* points to a possible explanation of this peculiarity. A large part of the papillomacular bundle passes from the disk directly to the macula without passing through the region of maximally impaired retinal nutrition. Furthermore, the macular area has its own source of blood supply both from the choroid and from the retina, by way of the macular branches.

Usually, the last part of the field to be destroyed is a small island in the temporal periphery (fig. 9 *B*). The reason for the preservation of this portion of the field may be deduced by referring to the diagram in figure 1 *A*. This area corresponds to the peripheral nasal portion of the retina, which is characterized by the least crowding of nerve fibers and is relatively avascular. Moreover, the fibers supplying this area do not pass through the zone of greatest retinal vulnerability. In this sense, the nasal periphery of the retina may be compared to the macular area.

The variability of field defects in patients with glaucoma is probably dependent not only on the pathologic process but also on the anatomic relation of the nerve fibers to the circulation.

The value of understanding the mechanism of the evolution of the field associated with glaucoma is not purely academic. In many cases, it enables one to predict the probable direction which future changes in the fields will take. It emphasizes the importance of the role played by the progressive arcuate scotoma in determining the pattern of peripheral loss of field. This phase will be the subject of a future communication.

SUMMARY

Approximately 2,000 visual fields in 350 cases of primary glaucoma were studied and classified.

The development of the characteristic field changes was analyzed by breaking down these defects into their component units, namely, the arcuate scotoma, the nasal field defect and what we term the juxtaceeal step.

It is shown that a relationship exists between the circulatory and the neural elements of the glaucomatous field and that most defects result from a mixture of these two components in varying quantitative combinations.

The concept outlined in this paper has prognostic value.

667 Madison Avenue.

ENTROPION IN INFANCY CAUSED BY FOLDING OF THE TARSUS

Report of a Case

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DEBRECEN, HUNGARY

REPORT OF CASE

An infant, born on Dec. 22, 1946, was brought to the clinic on Jan. 28, 1947. The mother stated that the child's eyes became inflamed on the third day after birth. She treated the eyes with camomile compresses, and the right eye recovered promptly, whereas the left eye remained closed and the discharge continued.

Examination showed that the right eye was normal except for redness of the conjunctiva and slight roughness above the convex tarsal margin.

The margin of the lid of the left eye was fully turned, resembling the picture of spastic entropion. The conjuctiva was diffusely reddened, with a smooth surface. In the center of the cornea there was a deep, round, sharp-edged infiltration, 3 mm. in diameter and of torpid character. The whole corneal surface showed a superficial haziness. Bacteriologic examination revealed no pathogenic organisms.

The entropion was unusual. Spastic entropion does not occur in the first weeks of life. There is a well known congenital form of turning in of either or both lids, caused by the so-called epiblepharon, in which the possibility of muscular overaction may be a secondary factor; but in this form the entropion remains partial, and the eyelashes only are turned in, not the whole lid.

The real nature of the entropion came to light when the lid was everted, which was done with difficulty. An edematous, bulging cul-de-sac appeared, exposing a tarsus fully folded in a horizontal direction. When the lid was replaced in its previous position, the anatomic cause of the inversion was easly evident; the tarsus, being the skeleton of the lid, was folded like two closed leaves of a book (fig. 1). The line of folding ran along the horizontal middle line of the tarsus. There was no pathologic change in the tarsal surface, not even a whitish or reddened line; the tarsus looked as though it might have been freshly twisted between the fingers.

By pressing on the skin of the lid with the finger against a lid plate, one could smooth out the tarsus. The result, however, did not last, and in a few minutes the tarsus curved in again and the entropion reappeared.

Obviously, some force had folded the sound tarsus and had kept it in that position for weeks. It had become accustomed to its new form, and a short period of straightening could not correct the deformity. This explanation suggested the operative solution of the problem: The tarsus must be kept in redressed position for a few days; this should be accomplished without deeper intervention.

A lid plate was introduced into the upper cul-de-sac, with pressure against the lid, and the tarsus was thus smoothed out. Then a gauze roll, 4 mm. in

From the University Eye Clinic.

thickness, was placed on the lid above its margin and fixed with two knotted mattress sutures (fig. 2 *A*). The sutures were inserted on both sides of the roll, deep enough to take up the tarsal tissue. Thus, the tarsus was kept in a straightened position until the sutures were removed (fig. 2 *B*).

Five days later the sutures and the roll were removed. This period was sufficient to reaccustom the tarsus to its normal, straightened position. The entropion

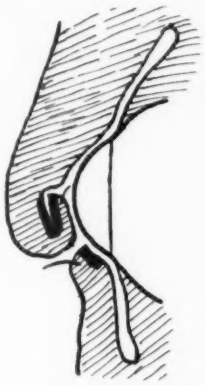

Fig. 1.—Cross section of the entropion.

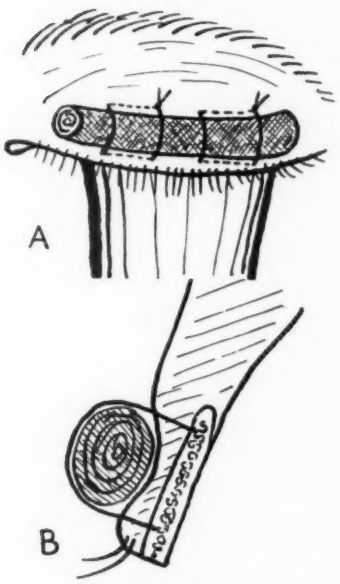

Fig. 2.—*A*, operative correction of the tarsus by two mattress sutures; *B*, cross section of the operation.

disappeared, and the cornea cleared up except for the central infiltration, which developed into a macula.

If this solution had not proved correct, and if the entropion had reappeared, I had planned to perform Kuhnt's tarsectomy, removing the upper broken part of the tarsus.

I believe that the inversion was produced as follows: The severe inflammation caused infiltration and edema of the upper fornix. The bulging conjunctiva hung down as a relatively heavy weight on the convex tarsal margin (fig. 3 *A*). The levator muscle was temporarily paralyzed, and the tarsus, still soft and tender in the newborn infant, became folded. The fold, having existed for a few weeks, became fixed. When the edema disappeared and the levator muscle regained its power, the convex tarsal margin was drawn back into its original place; but the fold, being fixed, turned the margin of the lid inward (fig. 3*B*). Restoration did not seem possible without surgical aid.

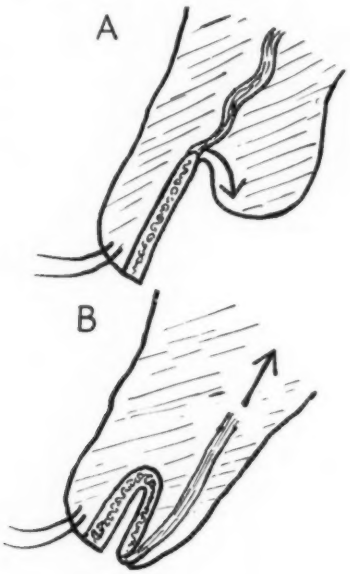

Fig. 3.—Explanation of the cause of the entropion, showing (*A*) breaking down of the tarsus and (*B*) regained tension of the levator muscle, which causes the folded tarsus to turn inward.

COMMENT

This strange form of entropion in infancy has apparently not been mentioned in the literature. Perhaps it is not so rare as it would seem. I myself remember having seen a few cases of entropion after purulent ophthalmia in infants, and in 1 case I performed a modified Hotz operation on both sides. I now believe that an origin similar to that just described existed in those cases. The case reported here was the first in which all the features of the entropion were clearly apparent and in which a hint of the origin was given and a simple method of operative correction indicated.

University Eye Clinic.

BOXING INJURIES OF THE EYES

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EVIDENCE is on record to the effect that among major sports boxing occupies a special position, since it deliberately aims at producing head injuries.[1] It has been pointed out that some of the more dramatic manifestations of these injuries are colloquially referred to by such terms as "knock-out," "grogginess" and "punch-drunk" and that, for this reason, it is not usually appreciated that such conditions indicate serious cerebral disorders. It is true that similar injuries occur in sports other than boxing, e. g., in football and wrestling; but here they are accidents, rather than sequelae of intentional acts.

This paper presents clinical data suggesting that a statement similar to that referring to cerebral trauma may be made with regard to ocular injuries in boxing.

ILLUSTRATIVE CASES

CASE 1.—M. L., aged 18, received a blow to the right eye during a boxing lesson at school. Almost immediately, vision in this eye became blurred. Ophthalmologic examination conducted on the same day revealed a hyphema filling two thirds of the anterior chamber. The blood was absorbed within eight days, but the pupil was flattened in its upper part. A peripheral tear in the iris, extending from 11 to 2 o'clock, was evident.

CASE 2.—This case, of a youth aged 17, is essentially similar to case 1.

CASE 3.—P. E., aged 18, noticed that vision in his left eye was blurred after a boxing match. Examination on the same day revealed visual acuity of 6/12 and small tears on the lateral edge of the left pupil, which was semidilated. Gonioscopic examination (Goldmann) revealed a small, fresh area of cyclodialysis of traumatic origin, situated opposite 2 o'clock, in the angle of the anterior chamber. During the subsequent fourteen days the tear closed gradually.

CASE 4.—G. G., aged 23, received a severe blow to his left eye while boxing. He subsequently observed that the lower part of the visual field was blacked out. Four weeks later a peripheral area of traumatic choroiditis of recent origin was

From the Medical Research Committee, National Advisory Council for Physical Education.

1. Jokl, E.: The Medical Aspect of Boxing, Pretoria, Union of South Africa, J. L. van Schaik, Ltd., 1941.

found in the upper part of the left fundus. Five months later the diagnosis of detachment of the retina, extending from 11 to 2 o'clock, was made. Two attempts at surgical treatment failed; and when he was last seen, a year after the boxing injury, a cataract was beginning to form.

CASE 5.—P. L., aged 30, was struck a severe blow on his left eye during a boxing match. Within a month the whole left retina became detached. An operation was performed in Switzerland, with unsatisfactory results. Two years after the injury the retina was still detached and lying in loose folds. No tear could be located.

CASE 6.—P. J., aged 16, was hit in the right eye during a boxing match. At an ophthalmologic examination fourteen days later, a vertical white area of retinal edema was seen. Three weeks later a choroidal tear was evident in the interior temporal part of the fundus. Two years later the diagnosis of a flat, circumscribed retinal detachment was made. Surgical reposition was successfully carried out. The retina has since remained in position, for eighteen months.

CASES 7 and 8.—Two additional cases of choroidal tear in boys aged 14 and 15 years, respectively, were essentially similar to the preceding cases. In both the tear was in the macular region, and visual acuities were as poor as 6/24 and 6/36, respectively. No retinal detachment appeared in the course of more than nine months.

CASE 9.—J. O'C., aged 39, a teacher, was demonstrating dodging in the boxing ring when his opponent hit him in the right eye. Within an hour he could not see with that eye. An extensive hemorrhage in the vitreous was observed; this cleared within a year, though at this stage visual acuity was still reduced to 6/18. Widespread macular changes were present. General examination revealed early arteriosclerosis and slight hypertension.

CASE 10.—During a boxing bout, H. R., aged 17, received a blow on the left eye, with the result that vision in this eye became blurred about an hour after he received the blow. At examination on the following day it was evident that he had unilateral keratoconus and that the blow had ruptured Descemet's membrane, with resultant edema and irritation of the eye. This condition lasted four weeks. The end result was slight scarring below the apex of the corneal cone.

SUMMARY

Ten cases of ocular injury due to blows incurred in "regulation" boxing are placed on record. Boxing occupies a special position among major sports in that it deliberately aims at producing head injuries.

New Standard Bank Building.

USE OF VASODILATORS IN SYPHILITIC ATROPHY OF THE OPTIC NERVES

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The causes of atrophy of the optic nerve are many and diverse. They include such unusual conditions as profuse hemorrhage and thallium poisoning, as well as more common causes, such as chronic glaucoma and cerebral tumor. In many cases the cause is a primary vascular lesion, angiospastic in nature, which occurs with acute retrobulbar neuritis, tobacco amblyopia and closure of the central retinal artery.

The present article will not be concerned with atrophy of the optic nerve due to any of the aforementioned factors, but will be limited to syphilitic atrophy of the optic nerve. It is possible for tobacco, or glaucoma, or a cerebral tumor to cause optic nerve atrophy in a patient who has syphilis. However, with the help of the history, the ophthalmologic examination, the neurologic examination, the Wassermann test, the roentgenogram of the skull and a study of the visual fields, it is usually possible to eliminate other causes of the atrophy and establish the diagnosis of syphilitic atrophy of the optic nerve.

The outlook for improvement, or even for maintenance, of vision in cases of syphilitic atrophy of the optic nerve is poor. In many cases the disease progresses to total blindness with or without the use of specific therapy. This is an instance in which knowledge of the causative factor (i.e., syphilis) or of the drug (i.e., arsenic) which is known to cure the disease is of little or no value in combating one of the most serious complications of the disease. This state of affairs recalls to mind Conklin's statement that first causes are like the vestal virgins—sacred but barren.

The various types of therapy recommended for syphilitic optic nerve atrophy are unphysiologic, to say the least. Gifford[1] mentioned spinal drainage with the intravenous injection of arsphenamine; the Swift-Ellis method (intraspinal injection of arsphenamized serum);

Presented at the One Hundred and Forty-First Annual Meeting of the State of New York Section of Ophthalmology and Otolaryngology, May 8, 1947.

1. Gifford, S.: Ocular Therapeutics, ed. 3, Philadelphia, Lea & Febiger, 1942, pp. 334-339.

Suker's method of injection of mercury bichloride into the lateral ventricle; Gifford and Keegan's modification of Suker's method, in which the injection is made into the cisterna magna, and the production of hyperthermia with the use of injections of foreign protein, malarial inoculations, the fever cabinet or the injection of sulfur.

Intensive therapy with certain arsenicals, such as sodium arsanilate ("atoxyl") and tryparsamide, is contraindicated, according to some observers, because these drugs at times seem to induce the onset of optic nerve atrophy or to hasten its progress if it is already present.

Many of the therapeutic procedures here mentioned are in the nature of blitzkrieg therapy, in which the body as a whole is subjected to sudden and violent physiologic changes. Fatalities are not unknown, and serious complications secondary to the treatment have been often reported.

PATHOLOGY, PATHOGENESIS AND TREATMENT

Moore and Woods[2] mentioned that pathologic changes usually occur in the intracranial portion of the optic nerves distal to the chiasm. Degeneration occurs first in the marginal fibers of the nerves. There are thickening and perivascular round cell infiltration of the overlying membranes (especially the pia) and of the connective tissue septums of the nerve.

Among the theories of the pathogenesis of syphilitic atrophy of the optic nerve are the following:

1. The atrophy is due to the coexistence of syphilis and lymphogranuloma venereum. This theory has no foundation in fact.

2. The optic nerve atrophy depends on a nutritional disturbance of the optic nerve, due to syphilitic involvement of the blood vessels to the optic nerve. Abadie published several papers on this theory between 1924 and 1932. He expressed the belief that degeneration of the nerve fibers was due to an ischemia produced by spasm of the arterial walls, due either to syphilitic inflammatory tissue or to involvement of their sympathetic nerve supply. I shall return to this theory later, but I mention here that Moore and Woods asserted that this theory was ill founded.

3. The optic nerve atrophy depends on a disturbance of the normal relations of systemic blood pressure, retinal blood pressure and intraocular tension, with resultant disturbances in the nutrition of the optic nerve or retina.

Lauber and Sobanski have been the most ardent proponents of this theory. Their treatment consists in raising the general blood pressure by injections of epinephrine, ephedrine or atropine and in lowering the intraocular tension with pilocarpine, or by cyclodialysis in some cases.

2. Moore, J. E., and Woods, A. C.: Am. J. Ophth. **23**:1 (Jan.) 1940.

Sobanski[3] reported the results of this treatment in a series of 37 patients. Thirteen eyes were blind before treatment was started. After treatment, of the remaining 61 eyes, 40 showed improved vision, 11 no change and 10 deterioration of vision. Arruga[4] treated 15 patients by this method; only 3 had improved vision.

Moore and Woods stated the belief that this theory is unsupported by the observed facts.

4. The optic nerve atrophy depends on meningeal inflammation with the development of opticochiasmal arachnoiditis, which constricts the optic nerve or its blood supply. Moore and Woods expressed the belief that this theory may explain an occasional case.

5. The optic nerve atrophy is due to the combination of nutritional (vitamin) deficiency and neurosyphilis. Moore and Woods stated that this theory offers a fertile field for further experimentation.

In a later communication, Moore and Woods[5] discussed the results of the conventional forms of treatment of this condition. Finally, in a statistical analysis of 250 cases of treated syphilitic optic nerve atrophy, Moore, Woods, Hahn and Sloan[6] concluded that adequate treatment of early syphilis almost completely protects against the development of optic nerve atrophy and that of untreated patients with optic nerve atrophy, almost 65 per cent are blind within three years of the onset and nearly 90 per cent are blind after twelve years. Subdural therapy precipitated blindness in 10 per cent of the patients so treated. Of patients subjected to malarial therapy, only 18 per cent were blind after three years and no other cases of blindness occurred within fifteen years.

According to Lehrfeld and Gross,[7] the prognosis is poor in all cases of syphilitic atrophy of the optic nerve. They reported on 91 patients who were followed from five to eight years. These patients were divided into three groups.

The first group received no treatment for the optic nerve atrophy. All were blind, or nearly blind, on admission to the clinic. Of these, 74.9 per cent were blind within three years of the onset of symptoms, and all were blind after five years.

The second group received routine antisyphilitic therapy. Of these, 23.8 per cent were blind within three years, and all were blind eight years after the onset of symptoms. The third group received a special form of treatment, such as induced fever or subdural therapy. Of this group, 28 per cent were blind in less than three years and all were blind at the end of eight years.

3. Sobanski, J.: Klin. Monatsbl. f. Augenh. **97**:1 (July) 1936.

4. Arruga, H.: Klin. Monatsbl. f. Augenh. **97**:308 (Sept.) 1936; Treatment of Atrophy of the Optic Nerve, abstracted, Arch. Ophth. **18**:168 (July) 1937.

5. Moore, J. E., and Woods, A. C.: Am. J. Ophth. **23**:145 (Feb.) 1940.

6. Moore, J. E.; Hahn, R. D.; Woods, A. C., and Sloan, L.: Am. J. Ophth. **25**:777 (July) 1942.

7. Lehrfeld, L., and Gross, E.: Am. J. Ophth. **21**:435 (April) 1938.

Lehrfeld and Gross expressed the belief that ophthalmologists must look in other directions for newer methods of treatment.

Bruetsch,[8] who examined the visual pathways of 70 patients with various types of syphilis of the central nervous system, concluded that the lesions in the optic nerve were due to an inflammatory process and that malarial therapy was the most efficacious type.

However, it seems to me that the almost complete absence of foci of spirochetes in the optic nerves in the cases reported by him and by others is indirect proof that the condition is not primarily inflammatory.

Biffis[9] reported on the autopsy observations in a case of dementia paralytica in which the optic nerves were involved. He stated the belief that the degeneration in the optic nerves was due to sclerosis of the capillaries supplying the septums of the nerve. The condition of the arterioles was not mentioned.

The most recent article on the treatment of this condition is that by Knight and Schachat.[10] They reported 19 cases of syphilitic optic nerve atrophy in which, in addition to adequate antisyphilitic chemotherapy, treatment in the Kettering hypertherm was given. In 2 of the cases "typhoid drip" therapy was also employed. In 4 of the cases some improvement occurred, as follows:

CASE 1: Vision improved from 20/20 to 20/15 in each eye, and there was an increase in the size of the peripheral fields.

CASE 6: Vision improved in one eye from perception of hand movements to 4/200.

CASE 8: Vision improved from perception of light to 3/200 in each eye.

CASE 17: Vision was unchanged, but an increase occurred in the extent of the peripheral fields.

In 7 cases there was an arrest of the clinical progression of the disease, and in 6 cases there was no arrest or the onset of symptoms actually seemed to have occurred during therapy. The duration of improvement was not stated for any of these cases.

Briefly, in 21 per cent of their cases there was slight improvement in visual acuity or in the fields, and in 37 per cent, arrest of symptoms.

Vascular Basis of Syphilitic Optic Nerve Atrophy.—Because most of the treatments in vogue for syphilitic optic nerve atrophy consist in major unphysiologic insults to the body, because therapy directed against the spirochetes is inefficient and is sometimes followed by rapid loss of vision and because most of the newer types of therapy involve expensive hospitalization and loss of time for the patient and are not without danger, it would seem that a revised therapeutic approach, based on the work of Abadie and others, is indicated.

8. Bruetsch, W. L.: Malaria Therapy in Syphilitic Primary Optic Atrophy, J.A.M.A. **130**:14 (Jan. 5) 1945.

9. Biffis, A.: Ann. di ottal. e clin. ocul. **65**:1 (Jan.); 105 (Feb.) 1937.

10. Knight, H. C., and Schachat, W. S.: Arch. Ophth. **35**:271 (March) 1946.

The words of Foster Kennedy are especially signficant. In 1938, he stated[11]:

> It is common knowledge that vascular accidents occur in the brain in the course of untreated luetic infections. The very fact that many of these episodes are rapid to occur and clear up without treatment is evidence in favor of the possibility of angiospasm being the causative mechanism. Surely, luetic invasion of cerebral blood vessels must at times be an irritation adequate to set up local reflex angiospasm in these vessels.

This is probably true not only of the brain but also of the eye and its adnexa. Several years ago I[12] carried out treatment in 3 cases of paralysis of various ocular muscles and 2 cases of acute iritis in which the Wassermann reaction was 4 plus. In all 5 cases intensive vasodilator

Fig. 1 (case 1).—*(A)* Field of left eye on June 5, 1935, prior to onset of treatment with vasodilator drugs. The right eye was blind. *(B)* Field of left eye on Aug. 2, 1935, after treatment. The functioning field was definitely enlarged. Vision was improved.
In this figure, and in the accompanying figures, illumination was 10 foot candles.

therapy without the use of (specific) antisyphilitic therapy effected a rapid cure of the ocular lesions.

Mawas and Pinheiro[13] also reported a case of rapid loss of vision during a course of injections of tryparsamide. A cure was obtained with injections of acetylcholine. Dr. Franklin Bracken described a similar case to me several years ago in which vision improved somewhat with intravenous injections of sodium nitrite

Finally Pickworth[14] quoted Hawes to the effect that "the later manifestations of neurosyphilis must be regarded as only a result of the vascular disease."

REPORT OF CASES

During the past ten years I have treated 5 patients with syphilitic optic nerve atrophy with vasodilator drugs only. Although the results

11. Kennedy, F.: New York State J. Med. **38:**1441 (Nov. 15) 1938.
12. Duggan, W. F.: Tr. Am. Ophth. Soc. **43:**505, 1945.
13. Mawas, J., and Pinheiro, F.: Bull. Soc. d'opht. de Paris **49:**336 (April) 1936.
14. Pickworth, F. A.: J. Ment. Sc. **50:**76 (Jan.) 1941.

are not astonishing, yet, because of the hopeless prognosis in most cases of this disease and because of the relatively few favorable results reported to date, it is believed worth while to bring these results to the attention of other ophthalmologists.

CASE 1.—J. C., a man aged 60, was seen on Nov. 6, 1934, at which time vision was 20/200 in the right eye and 20/70 + 1 in the left eye. Argyll Robertson pupils were present; there was bilateral primary atrophy of the optic nerve; the knee jerk was absent on both sides; there was a questionable Romberg sign, and the Wassermann reaction of the blood was 4 plus. He was referred elsewhere for treatment but failed to report for antisyphilitic therapy. On June 5, 1935 he returned to the clinic. At this time the right eye was totally blind. Vision in the left eye was 20/100, and the field was limited to a small area near the fixation point and a tiny area temporal to the region of the normal blindspot (fig. 1 *A*).

Between June 6 and June 21, he received ten intravenous injections of sodium nitrite (100 mg.). On August 2, vision was 20/50 —2 and the field (fig. 1 *B*) was at least five times as large as it had been prior to treatment. The patient then disappeared from observation.

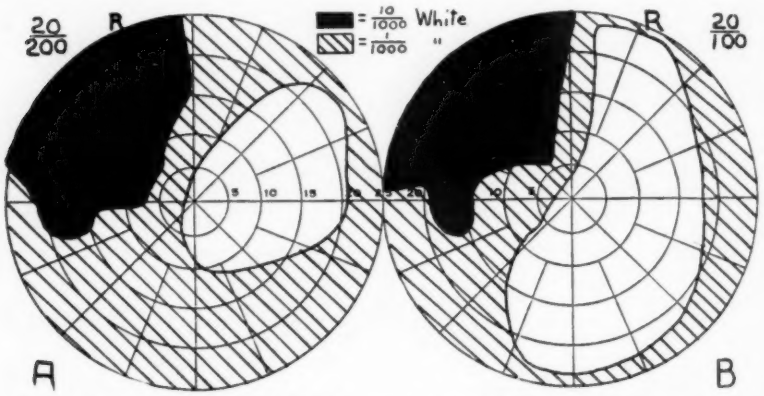

Fig. 2 (case 2).—*(A)* Field of right eye on Aug. 17, 1938, prior to treatment with vasodilator drugs. The left eye was practically blind. *(B)* Field of right eye on April 3, 1939, following vasodilator treatment. There was slight improvement in vision and in the field for 1/1,000 white.

CASE 2.—S. C., a woman aged 31, was first seen on Feb. 7, 1938, with the complaint of poor vision in the right eye for six weeks and in the left eye for several years. Vision was 20/200 in each eye. Argyll Robertson pupils were present, and there was bilateral primary atrophy of the optic nerve. The upper temporal quadrant of the right field was deficient, while in the left field only the upper nasal quadrant retained vision. The Wassermann reaction of the blood was 4 plus. A roentgenogram of the skull revealed no evidence of cerebral tumor.

The patient was referred to New York Hospital, where she received malaria therapy, intravenous injections of typhoid vaccine and, finally, treatment with a bismuth compound and the arsenicals. She returned to the clinic on Aug. 17, 1938, at which time vision was 20/200 in the right eye, but only 1/200 in the left eye. The right visual field (fig. 2 *A*) was essentially the same as it had been on February 7. The field of the left eye was almost completely obliterated.

Between Aug. 23, 1938 and March 27, 1939 the patient received thirty-three intravenous injections of sodium nitrite (100 mg.) in series of from three to ten daily injections each. Vision in the right eye had improved to 20/100 by September 16 (after the first twelve injections) and was maintained until April 3, 1939, after which the patient failed to return for follow-up observation. The field (fig. 2 *B*) showed slight, but definite, improvement in the isopter for a 1 mm. white test object at 1,000 mm.

CASE 3.—E. H., a woman aged 58, was seen at the clinic on Oct. 10, 1938, with the complaint that her lateral vision had been poor for two years. The onset occurred while she was receiving injections of tryparsamide at another hospital for syphilis of

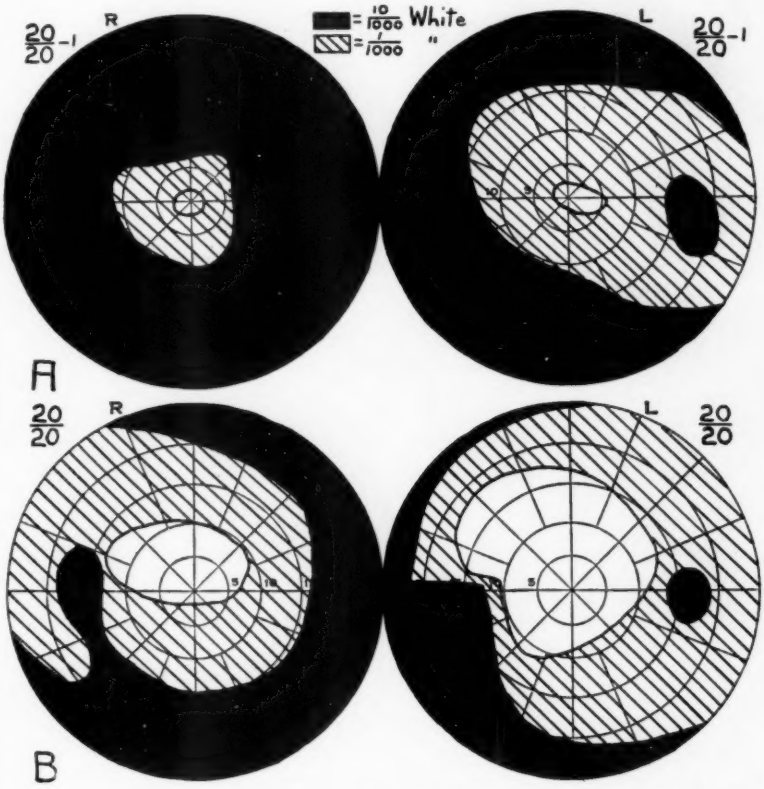

Fig. 3 (case 3).—*(A)* Fields of right and left eyes on Oct. 10, 1938, showing marked contraction of all isopters for white. Loss of visual fields occurred while the patient was receiving tryparsamide in 1936. *(B)* Fields of right and left eyes on Jan. 13, 1939, after vasodilator therapy. There was definite improvement in the visual fields.

the central nervous system. Vision was 20/20 —1 in each eye. Bilateral primary optic nerve atrophy was present. The retinal blood vessels were normal.

The fields (fig. 3 *A*) were greatly contracted for 10/1,000 white, while the field for 1/1,000 white was reduced to a tiny area around the fixation point.

Between October 11 and November 23, the patient received twenty-one intravenous injections of sodium nitrite (100 mg.) in three series of seven daily injections each. Fields taken at regular intervals showed steady and definite improvement. On Jan. 13,

1939, vision was 20/20 in each eye, and the fields (fig. 3 *B*) showed a notable enlargement of the isopters for 10 and 1 mm. white test objects at 1,000 mm. At this time the defect in the left field showed definite arcuate features.

In this case the loss of peripheral vision was attributed to tryparsamide.

CASE 4.—A. B., a woman aged 55, was seen on Jan. 16, 1939, with the complaint of poor vision in both eyes for ten years. She stated that vision had failed rapidly while she was being treated at another hospital for syphilis. Vision was 3/200 in each eye. Argyll Robertson pupils were present, and there was bilateral atrophy of the optic

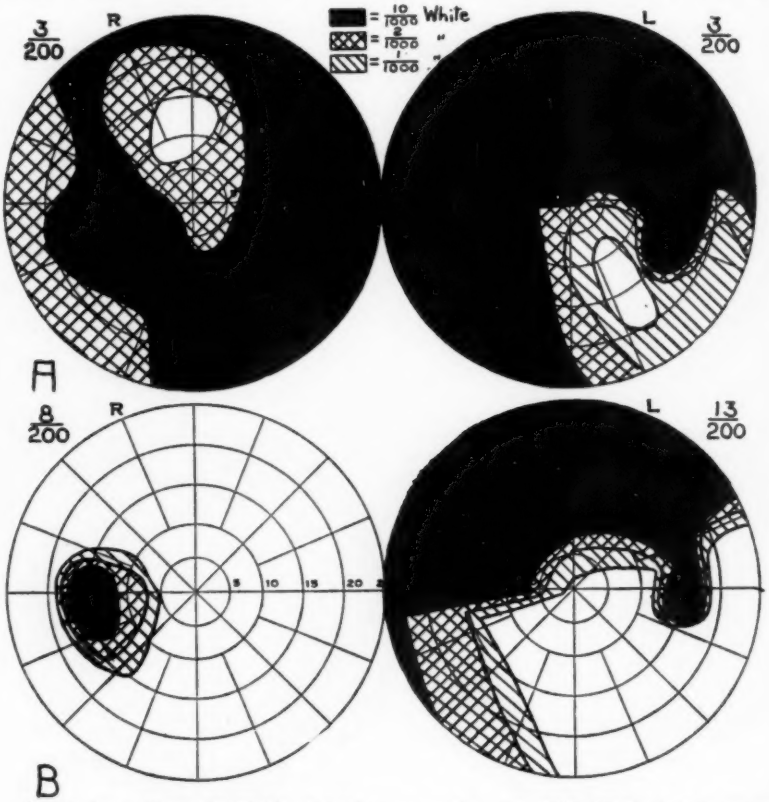

Fig. 4 (case 4).—*(A)* Fields of both eyes on Jan. 18, 1939. Vision had been poor for ten years. Visual failure occurred while the patient was undergoing antisyphilitic therapy. *(B)* Fields of both eyes on May 12, 1939, after therapy. Visions and fields showed definite improvement which was maintained until Sept. 20, 1939.

nerve. The retinal arteries were narrowed. Tangent screen fields (fig. 4 *A*) taken on January 18 showed a marked defect for 10/1,000 white. Small paracentral fields were present for 2/1,000 white in the right eye and for 1/1,000 white in the left eye. The Wassermann reaction of the blood was negative. Because of her impaired vision, the patient could not travel alone to the clinic.

The patient received twenty intravenous injections of sodium nitrite (100 mg.) between January 19 and February 9. On February 10 vision was 6/200 in the right eye and 5/200 in the left eye; the fields showed a little improvement. She was told to take ¼ grain (0.016 Gm.) of erythrityl tetranitrate U.S.P. twice daily and was given eleven

more injections of sodium nitrite between February 14 and February 24. She continued the use of erythrityl tetranitrate until May 12, at which time vision was 8/200 in the right eye and 13/200 in the left eye. A field taken on this date (fig. 4 *B*) showed considerable improvement over fields taken on her admission to the clinic, prior to the onset of treatment for the optic nerve atrophy.

The patient was seen last on Sept. 20, 1939, at which time her vision and fields had maintained the improvement manifested on May 12. At this time she was able to travel alone to the clinic.[15]

CASE 5.—G. M., an Italian aged 49, was seen on Nov. 6, 1943. He stated that in March 1942, two weeks after a lower tooth was extracted, vision had failed in both eyes. The left eye became entirely blind in three months.

The diagnosis of syphilis was made in May 1942, and he had received several courses of antisyphilitic chemotherapy.

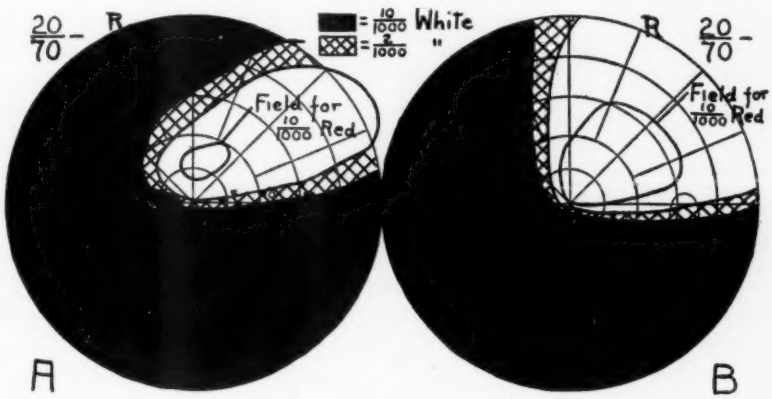

Fig. 5 (case 5).—*(A)* Field of right eye on Nov. 6, 1943, prior to the onset of therapy. The left eye was totally blind. *(B)* Field of right eye on Dec. 9, 1944, after vasodilator therapy. There was definite improvement in isopters for 10/1,000 and 2/1,000 white and for 10/1,000 red. Improvement was still present on Jan. 5, 1947.

Corrected vision in the right eye was 20/70 —1. The pupil was in middilation and did not react to light. The media were clear, and primary optic nerve atrophy was present. The retinal arteries were of normal caliber. A small field (fig. 5 *A*) was present in the upper nasal quadrant. The fact that a tiny field was present for 10/1,000 red was considered to be of favorable prognostic significance.

The left eye was totally blind. Primary optic nerve atrophy was present. The Wassermann reaction of the blood was negative.

As therapy, the patient received from 100 to 150 mg. of nicotinic acid, three times a day after meals, and ¼ grain of erythrityl tetranitrate at bedtime.

On Feb. 5, 1944 there was definite enlargement in his functioning field for 10/1,000 and 2/1,000 white. The field for 10/1,000 red improved more slowly and attained its maximum on Dec. 9, 1944 (fig. 5 *B*). Vision remained at 20/70 —1. On Jan. 5, 1947 the improvement was still maintained.

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15. Patients 1, 2, 3 and 4 were seen and treated at the Herman Knapp Memorial Eye Hospital.

The patient discontinued the use of vasodilators in January 1946. There was apparently no further loss of vision. He was in the habit of overindulging in whisky and volunteered the information that his vision seemed to improve temporarily after a drinking bout.

COMMENT

While only 5 cases of syphilitic optic nerve atrophy have been described, it is of interest that all 5 patients showed improvement with intensive vasodilator therapy. None became worse. Inasmuch as the time of follow-up observation varied from two months (case 1) to three years (case 5), a statistical analysis of the results would be futile.

However, it is my opinion that the improvement manifested in these cases corroborates Kennedy's[11] hypothesis that in syphilis angiospasm occurs in the arterioles of the central nervous system (including the visuosensory system). Since spirochetes are rarely observed in the optic nerves and treatment of the causative factor, syphilis, does not favorably influence the progressive loss of vision, a new approach to the problem of the treatment of syphilitic optic nerve atrophy is indicated. It is not beyond the bounds of reason to hint that syphilitic optic nerve atrophy may be a manifestation of chronic allergy or a problem in morbid vascular physiology.

It can be assumed, however, that syphilitic optic nerve atrophy is not identical with the atrophy occurring in the course of tobacco amblyopia or following acute retrobulbar neuritis, in which a complete return of vision to normal is possible after a relatively prolonged period of impaired vision. In cases of syphilitic atrophy of the optic nerve, the field defects are varied and sometimes bizarre. Moreover, even a slight improvement in the visual acuity or in the size of the functioning field is regarded as a favorable result. Since total blindness is a common occurrence in cases of syphilitic optic atrophy, any type of therapy which assists in maintaining the patient's vision is of definite value.

I believe that vasodilator therapy should be used with a large series of patients, preferably in one of the state hospitals, where a greater number of such patients should be available. Only after many of these patients have been treated and followed for an adequate time will it be possible to decide whether intensive vasodilator therapy compares favorably with the various therapeutic modalities at present in vogue.

Finally, if this type of therapy is shown to be of value in improving the function of the visuosensory system, it is not unreasonable to assume that similar therapy should be of value in treating other manifestations of syphilis of the central nervous system.

CONCLUSIONS

The results of vasodilator therapy in 5 patients with syphilitic atrophy of the optic nerve are described. No patient became worse during treatment.

All 5 patients showed improvement in the size of the functioning fields.

Three patients showed definite improvement in their visual acuity.

Similar therapy in a larger series of patients, with adequate follow-up observation, is indicated.

The ampules of sodium nitrite used in cases 1, 2, 3 and 4 were manufactured by E. Tosse & Co., a subsidiary of the Amfre Drug Company.

DISCUSSION

DR. IVAN J. KOENIG, Buffalo, New York: The treatment of syphilitic optic nerve atrophy with vasodilators has presented not only a new therapy, but possibly further knowledge of the pathologic nature, of this condition. Dr. Duggan's patients have all shown some improvement in visual acuity, which one must acknowledge, even though only 5 cases were presented.

In discussing syphilitic atrophy of the optic nerve and in evaluating its treatment, one must consider the causation and the pathologic condition. Igersheimer showed that the atrophy was accompanied with a slight perivascular round cell infiltration in the meninges of the optic nerve. Spirochetes were seen in these infiltrates, but rarely in the optic nerve, where focal lesions of degeneration were present.

The exact nature of the pathologic process is still in dispute. It is assumed that the optic nerve sheaths present an inflammatory infiltrate, which is followed by secondary degeneration of the optic nerve fibers and their ganglion cells. Foster Kennedy assumed that some vasoconstriction of the arterioles is present. This seems to be a logical conclusion, as such a construction could be produced by the inflammatory reaction. If this theory is true, the value of vasodilator therapy would be proved, and its use may account for the improvement in the color of supposedly atrophic disks.

Ophthalmoscopically, there are times when it is difficult to determine the amount of atrophy of the nerve, and when the question arises: Is this atrophy or pallor? Sloan and Woods reported certain field defects typical of tabetic atrophy with normal-appearing disks, which remained so for five years after changes in the fields had begun. Many clinicians and pathologists agree with Duke-Elder that "when actual optic atrophy has occurred, it is permanent." This statement of Duke-Elder's raises the question: How often can atrophy be recognized in sections of the optic nerve which shows pathologic pallor with the ophthalmoscope? Relief of the vasoconstriction may be the real answer to improvement in color, vision and field defects, but is it effective with true atrophy?

Many therapeutic measures may be used to produce vasodilation, among which are fever therapy (after its initial vasoconstriction), dia-

thermy, and administration of vitamin B complex, amyl nitrite, glyceryl trinitrate and acetylcholine, in addition to the drugs which Dr. Duggan has mentioned.

I have used sodium nitrite considerably in cases of disease of the optic nerve with pallor from some cause other than syphilis, with good results. I have not treated atrophy caused by syphilis with the drugs Dr. Duggan mentioned.

When asked to discuss this paper, I went over my records in search of cases of tabetic atrophy. I was surprised to find so few. I found 2 cases in which malarial treatment was given, with improvement in the field defects after treatment: In 1 case the visual improvement was maintained for six years, and in the other, for five years. This brings to mind a report of Woods and Moore, who claimed that 85 per cent of patients with one good eye (20/40) and a good visual field will show improvement in vision if given adequate malarial treatment. The remaining 15 per cent of patients will go blind in three years. Since malarial therapy is the accepted treatment of syphilologists, it might be wise to add vasodilators to their therapeutic armamentarium.

It is my feeling that syphilitic optic nerve atrophy will become a rare disease, for the treatment of early syphilis is being carried on more efficiently than ever before and this early treatment is the best way to avert the complication of optic nerve atrophy.

Before closing, I feel that some contraindications to sodium nitrite and erythrityl tetranitrate should be mentioned. I have used both these drugs, with therapeutic benefit, in other types of cases. Sodium nitrite does increase the intraocular tension in some cases of glaucoma and preglaucoma and should be used with discretion in such cases. Erythrityl tetranitrate, when used, frequently causes severe headaches, and the dose must be varied in some cases. A tolerance to vasodilators often becomes evident after two or three weeks' use, and a regimen of periods of rest with intermittent treatment is more advantageous than continued treatment with these drugs.

When using acetylcholine as a vasodilator, I have observed that the bromide salt gives a less severe general reaction than the chloride salt. In order to complicate a situation for more discussion, I should like to quote Best and Taylor, who, in 1945, stated that sodium nitrite causes vasoconstriction of the arterioles and that the fall in blood pressure is due to venous dilatation.

IMPLANT OF "VITALLIUM" TUBE IN TREATMENT OF STENOSIS OF THE LACRIMAL DUCT

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In the last two decades, the operation of choice in treatment of stenosis of the lacrimal duct has been dacryocystorhinostomy, with the more or less modified technics of Toti and Dupuy-Dutemps. Though the results of these operations have been encouraging, there is still a high percentage of failures, due mostly to alteration of the nasal mucosa in atrophic rhinitis and ethmoiditis and to technical difficulties in the operation. A much simpler procedure is the insertion of a "vitallium" tube into the bony lacrimal duct through the lower part of the sac, as advocated by Muldoon.[1]

"Vitallium" is an alloy composed of cobalt, 65 per cent; chromium, 30 per cent, and molybdenum, 5 per cent. It is free from chemical and electrolytic activities in human serum and when buried in human tissue does not produce any of the inflammatory reactions of other metallic foreign bodies.[2] It is used chiefly in bone surgery but is employed as in other surgical fields. The tube devised by Muldoon is 3 mm. in diameter and 18 mm. in length, with the lower end slightly tapered. I have used this model successfully in several cases of stenosis, but its failure in a case in which the tube, though properly placed, slipped into the bony lacrimal duct convinced me of the necessity of certain modifications.

In order that the implant may be held in its proper position, the new tube[3] is made with a holding loop 4 mm. from the opening of the tube into the lacrimal sac (fig. 1) and a small ring at the upper end. The loop serves a twofold purpose, first in permitting a surgical gut suture to be passed through the hole to be attached to the periosteum of the nasal bone, and, second, in widening the upper part of the tube to 5 mm., thus preventing its slipping down into the bony canal. Moreover, the tube is 24 mm. long, and about 4 mm. of its upper end is inserted into the lower part of the lacrimal sac.

The operation is usually performed with the use of local anesthesia, obtained by infiltration of the area of the lower part of the lacrimal sac with "solution of procaine hydrochloride 2 per cent with epinephrine" and injection of a few drops of cocaine,

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1. Muldoon, W. E.: Restoration of Patency of the Nasolacrimal Duct by Means of a Vitallium Tube, Am. J. Ophth. **28:**1340, 1945.

2. Venable, C. S., and Stuck, W. G.: Electrolysis Controlling Factor in the Use of Metals in Treating Fractures, J.A.M.A. **111:**1349 (Oct. 8) 1938: A General Consideration of Metals for Buried Appliances in Surgery, Surg., Gynec. & Obst. **76:**297, 1943.

3. This tube is manufactured by Austenal Laboratories, Inc., 224 East Thirty-Ninth Street, New York.

4 per cent, into the sac. The sac is washed with saline solution, and a Bowman probe is passed until it reaches the stricture in the duct. The purpose of this probe is to serve as a guide in the dissection and exploration of the duct. An incision, 1.5 cm. long, is made in the skin, starting at the lower part of the inner canthal ligament, which is left intact. The incision is carried down through the fibers of the orbicularis muscle and the deep fascia to reach the lower part of the sac, with the probe as a guide. A small incision is made in the sac and the bony canal is curetted, after which the "vitallium" tube is inserted and pushed down, leaving about 4 mm. of it, which is inserted into the lower end of the lacrimal sac.

The probe, which was partially withdrawn during the insertion of the "vitallium" tube, is now pushed down through the tube into the nasal cavity. A 000 surgical gut suture is passed through the holding loop and secured to the periosteum. Another small suture closes the sac over the tube, while the cutaneous wound is closed with silk. The probe is removed, and the lacrimal passages are irrigated with saline solution to ascertain their patency. A light compression bandage is applied, and the patient is discharged in twenty-four hours.

This procedure was used in 3 cases in which there were mucopurulent discharges from the puncta on compression of the sac.

Fig. 1.—Vitallium tube, La Rocca type.

REPORT OF TWO CASES

CASE 1.—A. D. F., a woman aged 54, complained of stenosis and purulent chronic dacryocystitis of the left eye of seven years' duration. The sac had been probed at several clinics and by private physicians. The patient was first seen in my office on Feb. 3, 1946, at which time there was a mucopurulent discharge on pressure on the region of the lacrimal sac; both canaliculi were present. Probing was unsuccessful and very painful because of an obstruction at the upper end of the bony lacrimal duct.

The patient was admitted on Feb. 15, 1946 to the New York Eye and Ear Infirmary, where a "vitallium" tube, of the Muldoon type, was inserted. Irrigation soon after the closure of the wound showed patency of the lacrimal passage. At the first dressing, a few days later, some discharge was still found in the sac, and irrigation showed that an obstruction had already formed. Probing through the tube was not attempted until about a week later. When it was found impossible to pass a probe through, a roentgenogram was taken (fig. 2), which showed displacement of the tube. The patient was readmitted on July 10. All attempts to raise the tube failing, a dacryocystectomy was performed, leaving the tube buried in the bony canal. Recovery was uneventful; epiphora persisted.

CASE 2.—R. V., a woman aged 62, had had epiphora and discharge from the sac of the right eye for the past two years. Only a few probings were attempted because of excessive sensibility. An occlusion was found at the beginning of the bony lacrimal duct. After several unsuccessful probings, the patient was admitted on July 2, 1946 to the

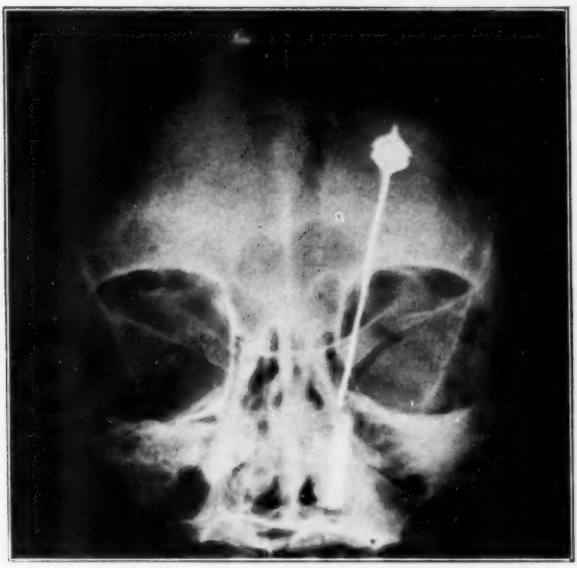

Fig. 2 (case 1).—Bowman's probe stops about 3 mm. from the upper opening of the tube.

Fig. 3 (case 2).—Probe passes through the sac and tube into the nasal cavity.

Columbus Hospital, where a "vitallium" tube, La Rocca type, was implanted, according to the technic previously described. She was discharged within twenty-four hours. At the first dressing, three days later, there was no discharge, and irrigation demonstrated the patency of the passages. A roentgenogram showing the tube in place with a Bowman probe passing through is shown in figure 3.

COMMENT

The implant of the La Rocca "vitallium" tube of the type described offers the following advantages:

1. The tube cannot slip into the nasal cavity because the upper end has a larger diameter than that of the bony canal.

2. It can be performed in any case of stenosis of the lacrimal duct with or without dacryocystitis, for, the patency being once established, the drainage takes care of the infection of the sac.

3. The operation is much simpler than the dacryocystorhinostomy.

4. Intranasal infections and atrophy of the nasal mucosa are not obstacles to implantation of the "vitallium" tube.

5. The operation can be easily performed with local anesthesia.

42 Fifth Avenue.

INTRAOCULAR PRESSURE IN CASES OF HEMORRHAGE OF THE RETINA

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My interest in the relation of intraocular pressure to hemorrhages of the retina was awakened by an article by Igersheimer,[1] and I began a systematic study of the tonometric readings of the eye in all patients sent to me for ophthalmologic examination with diseases in which complications involving the retina are frequent, the most important of these being retinal hemorrhage.

Igersheimer, after a brief discussion of the physiology of the eye, maintained that pressure outside the vascular walls, represented in the eyeball by the intraocular tension, may have an appreciable influence on the passage of fluid through the walls of the vessels. Only in certain conditions can this pressure be increased without the use of artificial methods. These conditions are fulfilled in the case of closed cavities, such as the eye or the cranium. I shall not discuss the observations and clinical details on which he founded his hypothesis, since the present paper does not purport to be more than a statistical contribution to strengthen or to correct his assertion.

I shall present the results obtained in a series of 215 patients, of whom 51 had hypertension but no retinal signs of vascular sclerosis, 129 had hypertension with retinal signs of vascular sclerosis and 33 had hypertension with definite renal involvement. One had arteriosclerosis but no hypertension, and another had retinal phlebitis with hemorrhage of tuberculous origin.

In a previous paper I showed the results obtained on 99 patients with diabetes. Thus, I have a total of 314 patients with or without retinal hemorrhage whose intraocular pressures have been systematically determined in order that the tonometric measurements may be correlated with the presence or absence of retinal hemorrhages.

Though the number of observations is small, it is large enough to give an idea of the relation of these two factors, and I can confirm to a great extent the opinion expressed by Igersheimer.

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1. Igersheimer, J.: Intraocular Pressure and Its Relation to Retinal Extravasation, Arch. Ophth. **32**:50 (July) 1944.

In my investigations, I followed the directions given by Vidal and Damel.[2] I consider that the tonometric readings obtained with the Schiötz apparatus indicate that 19 mm. represents normal tension, from 15 to 18 mm. physiologic hypotension and from 20 to 25 mm. physiologic hypertension. Values below 15 mm. indicate pathologic hypotension, and values above 25 mm., pathologic hypertension.

The tensions were determined at 9 to 11 a.m. Tetracaine hydrochloride, 0.5 per cent, was used as an anesthetic, and the measurement was made quickly and neatly once, with the Schiötz tonometer in order that the threshold of elimination should not be increased by the weight of the tonometer. The emotional state of the patient was taken into consideration.

In this series of 215 patients, 148 had no retinal hemorrhages (295 eyes were examined, as 1 patient had had an eye removed). The tonometric figures obtained for these patients are shown in table 1.

TABLE 1.—*Tonometric Readings on Eyes with No Retinal Hemorrhages*

Intraocular Tension, Mm.	No. of Eyes	Percentage of Total Series
0-14	8	2.7
15-18	57	19.3
19	94	31.7
20-25	125	42.3
25	11	3.7

TABLE 2.—*Tonometric Readings on 134 Eyes With Retinal Hemorrhage*

Intraocular Tension, Mm.	No. of Eyes	Percentage of Eyes (134)
0-14	5	3.7
15-18	49	36.5
19	37	27.6
20-25	42	31.3
25	1	0.7

Of these 215 patients, 67 showed retinal hemorrhages (134 eyes examined). The tonometric readings are shown in table 2.

Examination of tables 1 and 2 reveals the suggestive fact that the frequency of low readings is remarkably higher in eyes with retinal hemorrhages (40.2 per cent) than in eyes without such hemorrhages (22 per cent). It seems, therefore, that ocular hypotension (either physiologic or pathologic) predisposes the eye to hemorrhages of the retina.

In a series of 99 patients with diabetes on whom a similar study was carried out, 51 had no retinal hemorrhages (102 eyes examined), the tonometric readings being shown in table 3.

Of these 99 diabetic patients, 48 showed retinal hemorrhages (96 eyes). The tonometric readings are shown in table 4.

2. Vidal, F., and Damel, C. S.: Sistema neuro-vegetativo ocular: Tension ocular normal, Arch. de oftal. de Buenos Aires **19**:212 (April-May) 1944.

Examination of these tables confirms the salient observation on the first group, namely, that low tonometric readings (either physiologic or pathologic) are more frequent in eyes with retinal hemorrhage (38 per cent) than in eyes in which hemorrhage has not occurred (22.5 per cent).

When all the cases in which retinal hemorrhages were not present (cases of diabetes, hypertension and arteriosclerosis) are tabulated with all cases in which they occurred, the low tonometric readings show a similar greater frequency in the latter (table 5).

TABLE 3.—*Tonometric Readings on Eyes of Diabetic Patients With No Retinal Hemorrhage*

Intraocular Tension, Mm.	No. of Eyes	Percentage of Eyes (102)
0-14	4	3.9
15-18	19	18.6
19	21	20.5
20-25	54	52.8
25	4	3.9

TABLE 4.—*Tonometric Readings on Eyes of Diabetic Patients with Retinal Hemorrhage*

Intraocular Tension, Mm.	No. of Eyes	Percentage of Eyes (96)
0-14	10	10.4
15-18	27	28.1
19	23	23.9
20-25	29	30.2
25	7	7.2

TABLE 5.—*Tonometric Readings on Eyes of All Patients*

Intraocular Tension, Mm.	No. of Eyes	Percentage of Eyes
	Patients With Hemorrhages (397 Eyes)	
0-14	12	3.02
15-18	76	19.14
19	115	28.96
20-25	179	45.08
25	15	3.77
	Patients Without Retinal Hemorrhage (230 Eyes)	
0-14	15	6.52
15-18	76	33.04
19	60	26.08
20-25	71	30.86
25	8	3.47

The results of this investigation of 314 patients with diseases in which hemorrhage of the retina is a frequent symptom (627 eyes examined, as 1 patient had had one eye removed) may be summarized as follows: The intraocular tension (both physiologic and pathologic) is lower in patients with retinal hemorrhages (39.5 per cent) than in patients without such hemorrhages (22.1 per cent). From this, it may be concluded that a low intraocular pressure may predispose to the production of hemorrhage, for which reason a tonometric reading on patients with diseases in which retinal hemorrhages is a frequent complication is of definite value in the prognosis.

Although I do not wish to claim an absolute value for this conclusion, which may be invalidated by the relatively small number of cases

observed, it is evident that there is a certain relation between the intraocular tension and the appearance of retinal hemorrhage.

Since arteriolosclerosis tends to lower the intraocular tension[3] and phlebosclerosis to raise it, it is important in making a prognosis to know which of the two conditions is predominant in the case, as well as to determine the intraocular tension itself. With arteriosclerosis, the tension is lowered as the inflow of blood is decreased, owing to the diminished caliber of the arterioles; the decreased circulation, in turn, influences the production of the aqueous humor (if the theory is accepted that the latter is the result of dialysis). With phlebosclerosis, the tension is raised because of obstruction in the mechanism of elimination (venous capillaries and distributing veins).

In order to make this differentiation, the neuroarteriolar test devised by Vidal and Damel[4] and the neurocapillary test, proposed by Vidal and Malbran,[5] can be used, as well as the ophthalmologic examination.

The conclusions to be drawn from the present investigation are similar to those in my previous study:

1. The percentage of low ocular tonometric readings, both physiologic and pathologic, is suggestively higher in patients with hemorrhage of the retina than in patients in whom it does not exist.

2. Many of the cases in which retinal hemorrhages exist and the ocular tonometric readings are physiologically or pathologically high can be explained by the extent of the vascular alterations, against which the external pressure is insufficient to counterbalance or to withstand the passage of fluid.

3. In some cases a good vascular condition compensates for the predisposition revealed by low tonometric readings, and hemorrhage is not produced.

4. The prognostic value of the tonometric readings for patients whose vascular condition perdisposes to retinal hemorrhage is increased if the predominant type of vascular sclerosis can be ascertained when such sclerosis exists.

5. Low tonometric readings can be related to predominance of arteriosclerosis and high readings to predominance of phlebosclerosis.

Hospital de Caridad.

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3. Vidal, F., and Malbran, J.: Oftalmotono dinamico y arterioloesclerosis retiniana, Arch. de oftal. de Buenos Aires **20**:240 (June) 1945.

4. Vidal, F., and Damel, C. S.: Sistema neuro-vegetativo ocular: Test neuro-arteriolar, Arch. de oftal. de Buenos Aires **19**:297 (Aug.) 1944.

5. Vidal, F., and Malbran, J.: Sistema neuro-vegetativo ocular: Test neuro-capilar, Arch. de oftal. de Buenos Aires **20**:408 (Oct.-Dec.) 1945.

POSTMORTEM OCULAR PRESSURE

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The ancient Greeks, and Romans too, were well acquainted with the ocular phenomena of death. They are mentioned by Hippocrates, Galen and others. The artistic exhibition generally preceded the scientific description. One can see the postmortem immobility of the eyes in a turned-up position in the far famed picture of Guido Reni "Sain Sebastian," painted many hundreds of years before the scientific description. The first enumerations of postmortem ocular phenomena were made by Antoine Louis and, a little later, by Bichat. Most ancient investigators were interested only secondarily in scientific causes; their main motive was in agreement with the spirit of the age, to determine the real and absolutely sure sign of death. So great was the fear of cataleptic trance in those days that apprehension was not groundless. In this connection, interesting data may be found in the book of the famous Hyrtl.

Antoine Louis, in 1752, attributed an extraordinary significance to the sinking and softening of the eyeballs. According to his view, as long as the eye retains its normal firmness, the patient should not be declared dead, whatever other signs are present. The sinking and softening of the eyeballs prepare one for the subsequent putrefaction. It is natural that these statements did not stand without contradiction. Josat[1] (1854) emphasized that many patients survived the appearance of this phenomenon by nine days. Josat pointed out that the eyes, like other organs, attempt just before death to regain their former state, including the intraocular pressure. Ortila stated that in many cases of anaphylaxis the softened eyes became harder. In still other cases the formerly soft eyes became harder after death. The Marquis d'Ourches, in 1872, left a large sum for the discovery of a certain sign of death, and many prize essays arrived at the medical school. Devergie reported on these papers and discussed also the ocular pressure after death. He did not trust this ocular sign and noted many diseases in which a fall in ocular pressure was observable in life.

This paper appeared first in the Hungarian literature in 1939. The author was then assistant at the University Eye Hospital, Prof. L. de Blaskovics, Director. The author is not able to give the exact data for all the literature cited, as all his notes were lost during the war.

1. Josat, A.: De la mort et de ses caracteres, Paris, Germer-Bailliere, 1854.

Stellwag made the closest observation on postmortem changes in the eyes. He cited Coccius, who stated that if the glaucomatous eye was protected from desiccation it maintained its pressure for many days. Stellwag explained this by the rigidity of the sclera and the increased pressure in the intraocular veins. Albrand, an expert in postmortem ocular signs, stated that the ocular pressure becomes negative soon after death. He mentioned as a cause of this fall in tension the desiccation and the decrease in intraocular fluids. In ancient legal medicine, it was stated that the tension in the eyes was restored in the state of advanced putrefaction. Bouchut could not confirm this statement. Silbersteiner noted that the eye of a drowned man maintained its tension. This assertion was verified by the experiments of Bailliart,[2] Sedan[3] and Diaz Dominguez,[4] who placed the eye in distilled water and found that the pressure returned, whereas the pressure sank in a hypertonic solution.

Most of these observations were made before the time of the tonometer. Since the testing of ocular pressure by means of palpation is open to many errors, this method is to be applied only with care. Leber, who made exact manometric measurements on animal eyes, obtainted the following interesting results: On the death of the rabbit from bleeding, there was a sudden drop in ocular pressure, from 18.5 to 9 mm. of mercury. The pressure fell also at the moment of cessation of artificial respiration in curarized animals, even if it was high before, the average decrease being 8 to 12 mm. of mercury. Then followed a more gradual decrease. The cause was not the drop in blood pressure but the escape of the intraocular fluids.

Krause observed the enormous fall in tension in patients in diabetic coma and in cadavers. "It is generally thought that in moribund patients and in the cadaver a strong decrease in the tension is the rule, but this is not so. In recent years, I have measured the tension in more than two dozen moribund persons and cadavers and have never observed hypotony, such as occurs in diabetic coma." Krause's observations were made before the introduction of the tonometer.

Enucleation means the death of the eye; therefore, the measurement of tension in enucleated eyes is a suitable method by which to answer the question of ocular tension after death. Hamburger measured the tension just before and after enucleation. Of 9 nonglaucomatous eyes, 1 eye showed a decrease in pressure from the original 22 mm. of mercury to 16 mm., but the tension in the others fell to zero in nine minutes, the reverse of the condition in the 11 glaucomatous eyes, of which only 1 lost its tension entirely after enucleation, the others preserving 16 to 60

2. Bailliart: Imbibition de l'oeil enuclee. Rev. gen. d'opht. **40:**50, 1926.

3. Sedan, J.: Note sur l'imbibition d'un globe hypotone, Rev. gen. d'opht. **40:**89, 1926.

4. Diaz Dominguez, D.: Etude sur l'imbibition de l'oeil nuclee, Ann. d'ocul. **163:** 183, 1926.

per cent of the original pressure. In 1 case, even after four hours, the pressure measured 3 mm. of mercury.

Smith[5] found that blind glaucomatous enucleated eyes not only were hard at the moment of fixation but remained so a long time, proving that the high ocular pressure is not due to the blood pressure alone. Jacobson,[6] in 1884, stated that the glaucomatous eye retains its hardness after enucleation longer than the normal eye. Elliot, in the examination of 4 glaucomatous eyes, found that when the scissors were passed straight back to the optic nerve and free bleeding took place, the tension fell to 35 mm., whereas it previously had been 55mm. Smith, in his reply, mentioned a case in which the right (glaucomatous) eye twenty-fours after death was still harder than the other eye, and after enucleation was still harder than the fellow eye. Elliot observed that if a glaucomatous eye is thrown on the floor after removal it bounces.

I also measured the tension of the glaucomatous eye after removal, and I agree with the statements of Coccius, Stellwag, Priestley, Smith and others. There is no difference in the tension of the eye with primary glaucoma and that of the eye with secondary glaucoma. This observation was also shown in the tables of Hamburger.[7]

The measurement of tension in the enucleated eye does not meet with any obstacle. More difficult is its measurements with the eye *in situ*, in the orbit. In accordance with the observations in Valude's investigations and in mine,[8] the eyes are rolled up and fixed after death and the cornea is partly covered with the upper lid. Before the onset of rigor mortis, while it is easy to open the eyelids, the tonometer cannot be correctly placed.

The response of the tension in the death agony is also interesting, but its determination is not simple. The head is in constant movement from the forced inspiration, and the eyes are turned upward. In trying to bring the eyes down with the forceps, one produces a change in tension. For unconscious patients and for those who are not able to control the voluntry movements of the eyes, the Fick-Livschitz tonometer seems to me the most suitable. It has a spring and can also be applied to the sclera. Fernbach, at Hamburger's suggestion,[9] measured the tension on 4 cadavers fifteen to thirty minutes after death. The tensions in the eyes measured 0; 1.5 and 2; 2 and 2.5, and 5 and 5 mm., respectively.

My first case was that of a woman aged 68 with diabetes, who died of myocardial degeneration. Two days before death tension in the eyes measured 11 and 12 mm. of mercury; one minute after death it was 6 mm. of mercury in each eye; five minutes after death, 4.5 mm., and forty minutes after death, 1.5 mm.

5. Smith, P.: Glaucoma Problems, Ophth. Rev. **29**:289, 1910.

6. Jacobson, J., Sr.: Klinische Beitrage zur Lehre vom Glaukom, Arch. f. Ophth. **30** (pt. 1): 165, 1884.

7. Hamburger, C.: Grundsatzliches zur Lehre vom Glaukom, Klin. Monatsbl. f. Augenh. **87**:638, 1931.

8. Majoros, J.: Totenstarre der Augenmuskeln, Arch. f. Ophth. **134**:112, 1935.

The second case was that of a woman aged 58 with diabetes, who died of cardiac weakness, without coma or acidosis. The tension two days before death was 16 mm. in each eye, and two minutes after death it measured 2 and 4 mm. in the respective eyes.

The third case was that of a woman aged 72 who died of pulmonary embolism. Eight days before death the tension was 20 mm. in each eye; twenty minutes post mortem it was 15 and 13 mm., respectively.

In the first 2 cases I attempted, unsuccessfully, to measure the tension during the agony.

These cases confirm the observation of Leber that low ocular pressure occurs after death, not only experimentally in animals but also in man. The remaining pressure is lost over a relatively long period; there may be a difference between the tensions in the two eyes.

Preservation of the tension in the glaucomatous eye permits the important conclusion that the pressure in the glaucomatous eye is independent of the vascular pressure; i.e., the blood pressure exerts only a small, direct influence on the ocular pressure. When and why this independence begins in the glaucomatous eye is not understood. It is well known that the high ocular pressure falls with sudden weakness, showing that in some cases this independence of the ocular tension may break down abruptly.

In consideration of the factors which play a part in the postmortem fall of ocular pressure, it is logical to conclude that the primary fall is due to the loss of blood pressure. Koster showed that an increase of 0.007 in the ocular contents is followed by an increase in pressure of from 19 to 70 mm. of mercury. This statement is in accordance with Racevskij's[10] observation that the injection of 0.02 cm. of fluid raised the tension to 60 mm. of mercury. There is no question that the vitreous plays an important role in the postmortem ocular pressure.

SUMMARY

The ocular pressure falls at the moment of death, but some pressure remains. This residual pressure then disappears slowly. There may be a difference in tension between the two eyes. This postmortem change in the ocular pressure is not a safe and sure diagnostic sign of death. In numerous ophthalmic and general diseases the pressure is sometimes as low as it is in death. After enucleation the tension generally becomes zero. The glaucomatous eye retains its pressure after death and after enucleation. The primary decrease is due to the change in the vitreous. Tension in the eve with primary and that in the eye with secondary glaucoma act in the same way.

VIII Brody Sandor-u-6.

9. Hamburger, C.: Tonometrische Beitrage zur Lehre vom Glaukom, Klin. Monatsbl. f. Augenh. **67**:643, 1921.

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CONGENITAL HYPOPLASIA (PARTIAL APLASIA) OF THE OPTIC NERVE

BOURNE JEROME, M.D.

AND

H. WALTER FORSTER JR., M.D.

PHILADELPHIA

We are reporting 2 cases of a congenital anomaly which is rare when occurring in an otherwise normal eye. Scheie and Adler[1] (1941) reviewed the literature on the subject, finding 5 cases of partial aplasia of the optic nerve reported up to that time, and added 1 of their own. Another paper on this subject has since been published in Brazil.[2]

A brief review of the embryology of the optic nerve will facilitate understanding of the possible causes of the anomaly.[3] The optic vesicle becomes the optic cup, beginning at the 4.5 mm. stage of development. This is brought about by the invagination of the outer wall, the future retina, to approximate the inner wall, the future pigment epithelium. Coincidentally, the fetal fissure forms along the ventrolateral surface of the optic cup and stalk. Mesodermal tissue then invades the optic cup through the fetal fissure, filling the optic cup with embryonic blood vessels, the hyaloid system, and forming the primitive papilla. Fusion of the fetal fissure begins at the 10 mm. stage and is soon complete. At the 17 mm. stage the retinal ganglion cells appear, their axons piercing the primitive papilla and forming the neural elements of the optic nerve. The primitive papilla is thus enlarged by the cross sectional area of the nerve fibers to the size of the fully developed papilla. The axons of the retinal ganglion cells reach the optic chasm at the 18 mm. stage. Here, there is a partial decussation of the fibers, and at the 25 mm. stage they have reached the lateral geniculate body through the optic tracts. There are two possible explanations for the failure of normal development of the optic nerve, other ocular structures being normal:

From the Department of Ophthalmology, Hospital of the University of Pennsylvania.

1. Scheie, H. G., and Adler, F. H.: Aplasia of the Optic Nerve, Arch. Ophth. **26**:61 (July) 1941.

2. Rocha, H.: Hipoplasia do nervo optico, Arq. brasil. de oftal. **8**:1 (Feb.) 1945.

3. Mann, I. C.: The Development of the Human Eye, London, Cambridge University Press, 1928.

1. If for some reason the growth of mesoderm into the fetal fissure is delayed, the latter may fuse completely, thereby preventing any hyaloid, or later retinal, blood vessels from entering the eye. Complete aplasia of the optic nerve, with no papilla, retinal vessels or retinal ganglion cell layer, results.

2. If, for any reason other than defective blood supply, the retinal ganglion cells fail to develop, an abnormally small disk with normal retinal vessels may result, i.e., hypoplasia of the optic nerve. The visual field defects reported in some of the cases in the literature would presumably correspond to failure of development of the retinal ganglion cells, and the size of the papilla would depend roughly on the percentage of the axons of the ganglion cells present.

In the authentic cases reviewed and reported by Scheie and Adler[1] in which this anomaly of the optic nerve was present in otherwise normal eyes, clinical evidence supporting this theory of the mechanism of development of hypoplasia of the optic nerve is given. This anomaly may be unilateral or bilateral. These authors also reviewed a case reported by Krause (1920) which was apparently one of complete aplasia, without papilla or retinal vessel funnel, but the eye had 14 D. of myopia due to ectasia in the region where the optic nerve should have been. This observation suggests that complete aplasia of the optic nerve is not compatible with an otherwise normal eye. Scheie and Adler reported a total of 6 cases of hypoplasia—5 from the literature and 1 of their own.

REPORT OF CASES

CASE 1.—D. C., a Negro aged 24, a cow herder, was referred from the neurologic clinic on Dec. 11, 1946, because of nystagmus and poor vision. Treatment for epilepsy of four years' duration, with both petit and grand mal attacks, was being given, with recent notable reduction in the frequency of the attacks. The patient had been blind in his right eye since birth.

He stated that his birth had been normal and spontaneous. His only disease in childhood had been uncomplicated measles. The family history did not include cases of epilepsy, ocular disease or any condition pertinent to his present ailments. All 10 siblings were living and well.

Objective examination—physical, mental and neurologic—revealed no significant abnormality except for his eyes. The Kolmer and Kline tests of the blood for syphilis gave negative reactions. Electroencephalographic studies showed a general level of cerebral activity within normal limits.

Ocular examination revealed light perception only in the right eye, with visual acuity of 6/15, correctible to 6/15 + 3 with a —1.75 cyl. axis 35 in the left eye. Ocular rotations were full and the eyes straight. A transient, coarse ocular nystagmus of the type frequently seen with defective vision was present, and it increased in intensity during examination of the eyes. Both pupils reacted slowly to light and normally in accommodation.

On ophthalmoscopic examination the media appeared clear. The disks were nearly round, each being about two-thirds normal size. They appeared to be dead white ex-

cept on the nasal sides. The nasal side of the right disk was greenish white. The disk was obliquely placed and inclined steeply to the temporal side. The nasal side of the left disk was pale gray and similar in conformation to its fellow. A cilioretinal vessel emerged from its edge. Both disks had a heavy temporal pigment conus. After leaving the nasal side of the disk, the vessels destined for the temporal portion of the retina arched nasalward in wide sweeps before bending temporally. The vessels were of almost normal caliber but gave off few small branches. No abnormalities of the macular area or of the rest of the retina were noted in either eye.

The only field obtainable in the right eye was with a bright light, and this was smaller than normal in all meridians. Light projection was good in all meridians. The peripheral field of the left eye showed conspicuous contraction in the superior temporal sector to 1 and 10 mm. white test objects at 330 mm. The findings in the central field in this eye were consistent with the changes in the peripheral field, 2 mm. white and 20 mm. red test objects at 1,000 mm. being used. It seems reasonable to attribute these field defects to the deficiency in the formation of the neural elements evolving from the primitive ganglion cell layer, referred to in the introduction to this paper.

CASE 2.—W. D., a 6 month old white infant, was brought to us by his parents, who stated that he did not notice or follow objects and was apparently blind. Birth was at full term, and delivery was normal. Three other children of the same parents were all said to have normal vision.

General physical examination by members of the pediatric department of the hospital revealed no significant abnormalities. A roentgenogram of the skull was reported to be normal. External examination of the eyes and adnexa revealed nothing abnormal. Ocular rotations were full. The eyes were straight, and there were no nystagmoid movements. The pupils were round, equal and of moderate size. There were prompt direct and consensual light reflexes in each eye and good dilation with homatropine. Ophthalmoscopic examination revealed no appreciable refractive error and the media were normal. The optic disks were small, being about one-third normal size, round and cupped, with a gray pigment crescent nasally. The retinal vessels were present and normal in the number of branches, the caliber of both arteries and veins being somewhat smaller than normal. No lesion was seen in the fundus of either eye, and no definite macular abnormalities were visible with an ophthalmoscope.

In summary, there was no ocular abnormality except bilateral hypoplasia of the optic nerves.

COMMENT

These cases represent bilateral hypoplasia of the optic nerves. In case 1, the defect in the left eye was limited primarily to the inferior nasal quadrant of the retina, corresponding to the field defect mentioned, which was compatible with the 6/15 vision. In the right eye failure of development of the retinal ganglion cell layer was more generalized and vision was limited to light perception only. Retinal vessels were present in each eye.

In case 2, determination of the visual fields was impossible because of the age of the patient, but the defect was probably extensive bilaterally, since vision apparently was extremely poor. Light reflexes, however, were preserved, indicating some degree of retinal function.

This anomaly may be differentiated from atrophy of the optic nerve by the unusually small optic disk. In atrophy of the optic nerve in persons who have had normal embryonic development the disk is of normal size or, in extreme cases, only slightly contracted.

SUMMARY

Two cases of bilateral congenital hypoplasia of the optic nerve occurring in otherwise normal eyes are reported.

This anomaly is thought to be due to partial failure of development of the ganglion cell layer of the retina and consequent deficiency of neural elements in the optic nerve.

The defect is differentiated from atrophy of the optic nerve.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Third Pan-American Congress of Ophthalmology.—The Third Pan-American Congress of Ophthalmology was held in Habana, Cuba, Jan. 4 to 10, 1948, inclusive. All who attended felt that the meeting was a great success. Almost 1,400 ophthalmologists were registered, and every country in the Western Hemisphere was represented.

The following officers were elected to serve from 1948 to 1952: President, Dr. Conrad Berens; vice presidents, Dr. Esteban Adrogue (Argentina), Dr. Aniceto Solares (Bolivia), Prof. Ivo Correa Meyer (Brazil), Dr. John MacMillan (Canada), Dr. Santiago Barrenechea (Chile), Dr. Francisco Vernaza (Colombia), Dr. Alexis Aguero (Costa Rica), Dr. Miguel Branly (Cuba), Dr. Varas Samaniego (Ecuador), Dr. Miguel Medrano (Guatemala), Drs. Frederick Cordes and William Benedict (United States); secretary for area north of Panama, Dr. Thomas D. Allen; secretary for area south of Panama, Dr. Moacyr E. Alvaro; assistant secretaries for Latin America, Dr. Jorge Balza and Dr. Manoel Silva; assistant secretary for the United States, Dr. Brittain F. Payne; assistant secretary for Central America, Dr. Palomino Dena.

It was decided at the council meeting and ratified by the general assembly that the following permanent committees should be appointed:

Inter-American Federation of Ophthalmologic Societies.—President, Dr. William Benedict (United States); members: Dr. Jorge Malbran (Argentina), Dr. Aniceto Solares (Bolivia), Dr. Sylvio Abreu Fialho (Brazil), Dr. Italo Martini (Chile), Dr. Carlos Mena (Costa Rica), Dr. Jorge Suarez Hoyos (Colombia).

Committee on Lighting and Optics.—President, Dr. Magin Diez (Argentina); members: Dr. J. Pascal (United States), Dr. Roque Bellido Tagle (Peru), Dr. J. M. Penichet (Cuba), Dr. Rivas Cherif (Mexico), Dr. A. Cowan (United States), Dr. Caretti (Argentina), Mr. Tolman (New York).

Committee on Glaucoma.—President, Dr. Antonio Torres Estrada (Mexico); members: Dr. Peter Kronfeld (United States), Dr. Julio Raffo (Peru), Dr. Hilton Rocha (Brazil), Dr. Baudilio Courtis (Argentina), Dr. Esteban Adrogue (Argentina).

Committee for the Encouragement of Research in Ophthalmology.—President, Dr. Edwin Dunphy (United States); members: Dr. Phillips Thygeson (United States), Dr. Esteban Adrogue (Argentina), Dr. Paulo Filho (Brazil), Dr. Lech Jr. (Brazil).

Committee on Pharmaceutics.—President, Dr. Hughes (Chicago, United States); members: Dr. Roberto Pereira (Argentina), Dr. K. Swan (United States), Dr. Parker Heath (United States).

Society of "Amigos".—Honorary president, Dr. Francisco Belgeri (Argentina); president, Dr. Paulo Cesar Pimentel (Brazil); members: Dr. William Crisp and Dr. Shaler Richardson (United States), Dr. Magin Diez (Argentina), Dr. Santiago Barrenechea (Chile), Dr. Abelardo Zertuche (Mexico).

Committee on Establishment and Guidance of Ophthalmologic Societies.—President, Dr. Jesus Rhode (Venezuela); members: Dr. Frederick Cordes (United States), Dr. Durval Prado (Brazil), Dr. Roberto Pereira (Argentina), Dr. Oscar Horstmann (Cuba).

Committee on Legal and Industrial Ophthalomolgy.—President, Dr. Jorge Diaz Guerrero (Colombia); members: Dr. Ralph Lloyd (United States), Dr. Alberto Urrets Zavalia (Argentina), Dr. Santiago Barrenechea (Chile), Dr. J. M. Espino (Venezuela), Dr. Morris Davidson (United States), Dr. Jose A. Sena (Argentina), Dr. Tomas R. Yanes (Cuba), Dr. Eduardo Arce (Bolivia), Dr. Colombo Spinola (Brazil).

Committee on Standardization of Ophthalmic Hospitals and Clinics.—President, Dr. J. H. Dunnington (United States); members: Dr. Magin Diet (Argentina), Dr. Ivo Correa Meyer (Brazil), Dr. J. M. Penichet (Cuba).

Committee on Inter-American Medical Relationships.—President, Dr. R. Pacheco Lua (Guatemala); members: Dr. Daniel Kirby (United States), Dr. Derrick Vail (United States), Dr. Palomino Dena (Mexico), Dr. Sylvio Abreu Fialho (Brazil), Dr. Georgiana Theobald (United States), Dr. Olga Ferrer (Cuba).

Committee of Purchasing Section.—President, Dr. Rene Contardo (Chile); members: Dr. Paiva Goncalves (Brazil), Dr. Luis E. de Mora (Peru), Dr. Jorge Malbran (Argentina), Dr. Roberto Vazquez Barriere (Uruguay).

Contact Lens Center Committee.—President, Dr. Baudilio Courtis (Argentina); members: Dr. Arno Town (United States), Dr. Enrique Bertotto (Argentina), Dr. Daniel Silva (Mexico), Dr. J. Pascal (United States).

Committee on Orthoptics.—President, Dr. Avery Prangen (United States); members: Dr. Jorge Malbran (Argentina), Dr. Cesar Rodriguez (Peru), Dr. Raimundo Tartari (Argentina), Dr. J. Mendonca de Barros (Brazil).

Committee on Scientific Cinematography.—President, Dr. Hilton Rocha (Brazil); members: Dr. Gilberto Cepero (Cuba), Dr. A. Bedell (United States), Dr. Magin Puig Solanes (Mexico), Dr. Caretti (Argentina).

Committee on Trachoma.—President, Prof. Cesario de Andrade (Brazil); members: Dr. Jose R. Toja (Argentina), Dr. Roque Bellido Tagle (Peru), Dr. Paula Santos (Brazil), Dr. Phillips Thygeson (United States).

Bureau of Professors. — President, Dr. Jorge Valdeavellano (Peru); members: Dr. Derick Vail (United States), Dr. R. Rodriguez Barrios (Uruguay), Dr. Miguel A. Branly (Cuba), Dr. Alberto Urrets Zavalia (Argentina).

Committee for the Prevention of Blindness.—President, Dr. Alberto Vazquez Barriere; members: Dr. Tomas R. Yanes (Cuba), Dr. Sanchez Bulnes (Mexico), Dr. Natalicio de Farias (Brazil), Dr. Magin Diez (Argentina), Dr. C. Espildora Luque (Chile), Dr. Franklin Foote (United States).

Committee on Statutes.—Dr. Tomas R. Yanes, Dr. Moacyr E. Alvaro, Dr. Conrad Berens, Dr. Alberto Vazquez Barriere, Dr. Thomas D. Allen, Dr. Santiago Barrenechea.

Board of Censors.—President, Dr. Tomas R. Yanes (Cuba); members: Dr. Alberto Vazquez Barriere (Uruguay), Dr. Esteban Adrogue (Argentina), Dr. Enrique Cipriani (Peru), Dr. Derrick Vail (United States), Dr. Rene Contardo (Chile), Dr. Paulo C. Pimentel (Brazil), Dr. Luis Sanchez Bulnes (Mexico), Dr. Constantino Herdocia (Costa Rica).

Committee on Neuro-Ophthalmology.—President, Dr. Alejandro Posada (Colombia); members: Dr. Pedro Falcao (Brazil), Dr. Jorge Malbran (Argentina), Dr. Esteban Adrogue (Argentina), Dr. Frank Walsh (United States), Dr. Alfred Kestenbaum (United States).

Obituaries

HENRY SMITH, I.M.S.

1859-1948

Colonel Henry Smith died in his old home and birthplace, Clogher, Tyrone County, Ireland, on Feb. 28, 1848. He received his education at Queen's College, Galway, and, after graduating from the Royal University of Ireland with first honors, entered the Indian Medical Service in 1890. Dr. Smith served thirty years in the Punjab, principally in Jullundur and Amritsar, and in 1910 rose to the rank of Lieutenant Colonel, Chief Medical Officer of the province, Companion of the Indian Empire and Honorary Surgeon to the Viceroy. The extent of the daily activities which fell to the lot of a medical member of the Indian Medical Service was measured by his varied duties; he was in charge of the civic hospital and superintendent of the jail, was prepared to do autopsies and served as member of the plague commission and as supervisor and attendant of outlying health dispensaries. The work in general surgery was most varied, ranging from litholopaxy to excision of the superior maxilla, and in the Punjab there were many persons with cataract. The patients with cataract came to the hospital during a period of six weeks in the spring and again in the late fall, as governed by the climatic conditions. While the average yearly number of cataract operations in the hospitals in this province was usually about 300, in the hospital under Colonel Smith's management this number rose to 2,000 or 3,000 a year, so that during the cataract season 50 to 100 cataract operations were performed every day. With this enormous material, it is easily understood that a progressive surgeon soon found the old type of operation unsatisfactory, principally because of the resulting reactions from retained capsule and cortex and the frequent necessity for secondary operation. As the inadvertent, spontaneous intracapsular extraction gave such unexpectedly good results, Colonel Smith, following the work of Drs. MacNamara and Molroney, revived the intracapsular extraction, with the most important addition of control of the orbicularis muscle. Gradually, with his remarkable acumen and courage, he developed and publicized the intracapsular cataract operation, which in a modified form has become the accepted procedure of the present day.

A man of large stature, Colonel Smith was a fearless operator. With deft and sensitive fingers and a studied appreciation of the delicacy of

the anatomic structure of the eye, he applied pressure in his cataract operation with exact direction and control, so that the returning vitreous pressure ruptured the suspensory ligament according to the laws of hydrostatics.

He wrote many articles describing his method and a book which is a classic (Treatment of Cataract, Calcutta and London, Butterworth & Co., 1928), with illustrations by the late Dr. D. T. Vail, of Cincinnati. Besides the men of India, many surgeons from England, Europe and America visited the Colonel for inspiration and instruction, and found serious and generous welcome and encouragement.

After his retirement in 1921, he returned to India in 1925-1926, for one season, to devise a modification of his operation, which is fully described in a second edition of his textbook, and with which he believed all criticism which had sprung up was answered.

In 1898 Colonel Smith married Hester Dill Russell, a physician, also in the Indian Medical Service; they had two sons.

A man of original and independent thought, he often approached a problem in a way different from long-accepted methods and thereby aroused criticism. He was so thoroughly convinced of the correctness of his reasoning and so fervidly defended it that his strong personality frequently led to disputes and altercations in the press and at meetings, where he demonstrated a characteristically determined pugnacity. Any opposition to the intracapsular method aroused his fighting instincts, which perhaps often obscured the real issue.

Colonel Smith was a dominant personality who, by his faithful work, made a great name for himself in India and added to the prestige of that remarkable institution, the Indian Medical Service, which contributed so greatly to the distinction of the British rule. In ophthalmology he will always be remembered for his pioneer work in the development of the intracapsular operation.

ARNOLD KNAPP.

Col. W. F. Harvey, now of Edinburgh, has forwarded these reminiscences: "I first came in contact with Major Henry Smith in 1902, when, as Deputy Sanitary Commissioner of the Punjab, I was deputed to examine plague vaccine bacteriologically. He invited me to stay with him in Jullundur. I can say, truthfully, that it was an honor conferred on a junior officer by a great man, for he was indeed a great man, not only in mind but in body.

"He was a general, as well as an ophthalmic, surgeon. At his operations, in a small theater, the bazaar population would frequently be gazing in at the window. Over the tables a stoneware jar filled with dilute red mercuric iodide (1:3,000) hung from the roof, from which a small rubber

tubing could supply a continuous stream to the field of operation. Smith was a true follower of Lister, and his operations were successful. It was his habit also to smoke a cigar through the operation. 'If I have to lay down my cheroot, Harvey,' he said, 'it is a bad operation; and if my cheroot goes out, it is a damned bad operation.' No doubt the curiosity of sightseers turned many such jesting remarks into actual happenings.

"Many incidents and discussions dimly recur to my memory of those days when I lived with Dr. Smith in the Chhota Bari Dari, a bungalow belonging to the Maharaja of Kapurthala. Smith, for instance, at that time had little belief in the mosquito theory of malaria. He remembered being on service in the Bolan Pass and how, with unturned earth in the digging of trenches, epidemic malaria broke out among the troops. His views on night blindness and its successful treatment were, if I remember rightly, sound, and his argumentation was both logical and forcible. In his early days I think he had set out to be a lawyer. By the time I knew him he was not only logical but legal and, like most Irishmen, 'agin the Government.' His pet aversion was the government of India's attempt to regulate the amount of fees payable by patients for successful operation. Smith's name is linked just as firmly and rigidly to extraction of the lens in the capsule as Freyer's name is linked to the operation on the prostate. Colonel Smith was not the inventor of the intracapsular operation for cataract, nor did he claim to be; it is not too much to say that he developed and publicized the operation.

"A memorable occasion was the great Jonathan Hutchinson's visit to India to study leprosy. He stayed with the Colonel. Naturally, he was an enthusiastic admirer. The Colonel collected a goodly number of patients for his benefit, 40 cases that morning. Dr. Hutchinson, no longer young, became tired; so Dr. Smith told me to accompany him back to the bungalow. On the way, I said, 'Well, sir, what do you think of that operation?' In reply, he said: 'Well, I don't think I should recommend a beginner to start on it in preference to the old one; but if I were advising a young man who wanted to specialize either in cataract or in bladder surgery, I should advise him to come here to study.' "

Dr. C. B. Meding writes: "In an Indian bungalow, in a room 20 by 20 feet, about whose wall, except for a door and a window about 4 feet from the floor, ran a desklike shelf, on which lay, in order, an open volume of the 'Encyclopaedia Britannica,' an atlas and a dictionary, there stood the man I had traveled 10,000 miles to see, Col. Henry Smith, I.M.S. He turned to greet me, held out his great hand and said, smilingly, 'How much do you know about physiological optics?' I answered wisely, 'Nothing.' From that moment, until his death, I was, with many another, his pupil. We found example, instruction and guid-

ance under a tireless, kindly enthusiast. He presented ophthalmology with a jewel of surgery and lived to see its acceptance. 'Of such is the kingdom of medicine.' "

Col. C. H. Reinhold published the following note in the *British Medical Journal* (**1**:912 [May 8] 1948):

Not enough has been made in the short obituary notice in the *Journal* of April 17 (p. 765) of the pioneer work that Col. Henry Smith did in cataract surgery during the early years of the century, and the violent controversary which raged up and down India in ophthalmic circles in those days over extraction of the cataractous lens in its capsule. The operation is still widely practiced in India (or was, when I left there ten years ago), and in capable hands is continuing to give good results . . . Many surgeons from Europe and America came to sit at his feet and carried his technique and teaching back to their own countries. But his was not a one-track mind and his originality extended into other fields of medicine. When I and my contemporaries were being taught in the medical schools of the U.K. at the turn of the century to treat shock with stimulants and were pumping strychnine into our patients, he was already advocating morphine. He was a great man and ahead of his time as a thinker. I feel that I must pay this tribute to his memory as one who fell under his spell in Jullundur nearly forty years ago.

The following note is taken from the *Indian Pioneer,* the leading newspaper in India:

Colonel Smith has left India. Men may come and men may go, but men of the calibre of Colonel Smith do not come and go every day. It is unnecessary to comment on his world fame as an ophthalmic surgeon. He gave the world better, surer and safer eye sight. He had pupils from every land at his Jullundur and Amritsar clinics. Many who on arrival were skeptical of the numbers of ophthalmic and general surgical operations performed, carried home the story of their astonishment and admiration of a brilliant surgeon and a great man. All noted the rigidity of his ethical life, right was right and no number of wrongs made a right; truth was truth and no casuistry made falsehood into truth. He was plain, blunt, open and above board with everybody from sweeper to prince. His skill and kindness brought him into close contact with India's people. They named him Jullundur Smith and so he was known in every Indian village. No white man knew the people of the Punjab better, he loved them and they reciprocated. He was a great influence in the maintenance of the British raj. He was big, mentally, morally and physically and he operated on thousands upon thousands for two great Indian afflictions, cataract and stone. India mourns his going, the world honors him.

Abstracts From Current Literature

Biochemistry

ON THE PRESENCE OF HISTAMINE IN THE AQUEOUS HUMOUR. NILS EMMELIN and ERIK PALM, Acta ophth. **22**:117, 1944.

The authors give experimental data showing that in the aqueous of dogs, cats, rabbits and oxen a substance has been detected that causes contraction of guinea pig intestine. This substance resembles histamine in the following ways: The musclar contraction caused by aqueous resembles that caused by histamine. Aqueous produces bronchial constriction in the guinea pig. The substance is destroyed by boiling in alkaline, but not in acid, solution.

An increase in the histamine content of the blood plasma by intravenous injection of histamine does not increase the histamine content of the aqueous.

O. P. PERKINS.

Conjunctiva

ALLERGIC CONJUNCTIVITIS AND KERATITIS. A. MAGITOT, Ann. d'ocul. **178**:321 (Aug.) 1945.

The author states that the clinician sees many cases of conjunctivitis and keratitis in which the etiologic agent is neither a bacterium nor a virus. These conditions are considered inflammatory for lack of a better definition. The term allergy, however, connotes something different, and the purpose of the paper is to point out the significant differences.

The author's consideration of allergy, immunity and hypersensitivity is followed by a classification of the different types of allergy that occur. He discusses the allergic responses that occur in the ocular tissues, such as the immune-allergic reaction which can be produced in the cornea of experimental animals.

This discussion is followed by a description of allergic conjunctivitis. The acute form is characterized by pronounced edema and dilatation of the conjunctival vessels, and the subacute form by follicles, moderate edema and an eczematous lesion of the skin, such as one sees associated with the sensitivity to atropine. The third form consists essentially of hypertrophy of the conjunctival follicles. The allergic reaction seen in staphylococcic and streptococcic conjunctivitis is described.

Phlyctenular keratoconjunctivitis is discussed at length in the final section of the paper, and the various etiologic factors are considered. The author expressed the belief that phlyctenular keratoconjunctivitis in children is related to tuberculosis, but this does not signify that the lesion itself is tuberculosis. In adults the same type of lesion may occur but in most cases must be attributed to a different allergen.

P. ROBB MCDONALD.

Cornea and Sclera

THE INFLUENCE OF GENERAL METABOLIC AND NUTRITIONAL DISTURBANCES UPON THE RESISTANCE OF THE CORNEA. A. FUCHS. Am. J. Ophth. **30**:721 (June) 1947.

Fuchs remarks the strength and resistance of the cornea and discusses the following conditions which cause lowered coreneal vitality: lagophthalmos, cerebral hemorrhage, marantic corneal ulcers, keratomalacia, exophthalmic goiter and eczematous conjunctivitis. He believes that the basic condition in these is a striking diminution of the vitality of the connective tissue apparatus.

W. S. REESE.

THREE CASES OF INJURY OF THE LENS WITHOUT DEVELOPMENT OF CATARACTS. N. DISLER, Vestnik oftal., 1946, vol. 25.

A boy, aged 15, had a bilateral injury of the lenses with fragments of glass from an exploded test tube. The right lens became opaque within seven to ten days and was extracted. The glass fragment in the left lens was surrounded by the injured anterior capsule of the lens. Within a year the capsule around the foreign body became thicker, but the opacities of the lens adjacent to the site of the injury cleared and vision was 0.9 with a normal size pupil and 0.3 with the pupil dilated. This patient was observed for seven years. Most likely the foreign body firmly surrounded by the capsule of the lens closed up the hole in the lens without allowing the aqueous to penetrate the lens and produce a traumatic cataract. Since the eye remained quiet for seven years with good vision, there was no indication for surgical intervention.

In the second patient, the lens was injured with a small copper foreign body at 10 o'clock near the limbus. The lens became opaque along the route of the injury, and calcinosis developed. Vision remained 0.4 during one and one-half years of observation. The foreign body was floating freely in the vitreous.

The third patient, a young physician, had a small, transparent foreign body in the upper and inner part of the posterior capsule of the left eye. There was a small opacity in the anterior capsule with a firm synechia with the iris at the site of entrance. The eye was quiet during three years of observation.

Disler discusses the prognosis of traumatic cataract according to the changes observed with focal illumination and slit lamp (appearance of vacuoles) and the indications and contraindications to the removal of foreign bodies in the lens.

O. SILCHEVSKA.

TRANSPLANTATION OF AN ENTIRE CORNEA. P. RIISE, Acta ophth. **21**:26, 1944.

This is a case report of transplantation of an entire cornea to an eye wherein the cornea had sloughed out as a result of ulceration. After a year, the central and temporal parts of the implant were sufficiently clear to allow observation of the pupil. Vision was limited to hand movements.

O. P. PERKINS.

Experimental Pathology

LOCAL TREATMENT OF INTRABULBAR INFECTIONS: II. THE CLINICAL AND HISTOLOGICAL PICTURE OF THE STAPHYLOCOCCUS INFECTION. G. RONNE, Acta ophth. **22**:105, 1944.

The results of experimental injection of staphylococci into rabbit eyes are described. With the strain selected, a dose of 50 bacteria injected into the vitreous was sufficient to produce perforation of the eye in less than four days. The infection was characterized by considerable edema of the cornea, pronounced congestion and exophthalmos. These signs were all present on the second day. If the injection is made in the anterior chamber, there is intense iritis with hypopyon, together with early infiltration, ulceration and necrosis of the cornea. In most cases, however, the course is somewhat less malignant, and larger doses of organisms (ten to one hundred times as great) are required.

In the case of infection in the vitreous, the histologic picture is characterized by primary reaction on the part of the retina and ciliary body—changes occurring in the choroid only when this barrier has been broken down. Iris and anterior chamber remain intact and free from bacteria for a relatively long time.

O. P. PERKINS.

General

MEDICAL ASSISTANCE AT PROFESSIONAL LEVEL. P. HEATH, Am. J. Ophth. **30**:992 (Aug.) 1947.

Heath concludes that the development of a professional group of ophthalmic associates will contribute substantially to medical care for ophthalmologic conditions. He suggests a program that can be created within existing educational facilities.

W. S. REESE.

General Diseases

AMAUROSIS ASSOCIATED WITH PERFORATED AND BLEEDING DUODENAL ULCER. D. FORGARASI, Wien. klin. Wchnschr., **58**:716 (Nov. 29) 1946.

Forgarasi observed blindness in a man aged 49 with bleeding and perforated duodenal ulcer. The patient had had gastric disturbances almost constantly since 1940. Blindness following loss of blood had received little attention in the surgical literature, but in the ophthalmologic literature a considerable number of such cases are reported. In men, usually in the fourth and fifth decades of life, it is generally hemorrhage in the gastrointestinal tract that is responsible for this form of blindness. In women, however, this form of amaurosis is usually observed after profuse loss of blood incident to childbirth or abortion. Amaurosis has been observed also after venesection. The degree of visual disturbance varies, but loss of vision is usually complete. For treatment blood transfusions have been recommended, but liver and iron preparations, as well as acetylcholine and strychnine, have been used. The prognosis is usually unfavorable.

J.A.M.A., W. ZENTMAYER.

PRESENT DAY CONCEPTION OF THE WEVELOPMENT OF INTRAOCULAR TUBERCULOSIS. A. SAMOILOV, Vestnik oftal. **25**:3, 1946.

Samoilov, an authority on intraocular tuberculosis, analyzes the previous concept of the etiology of intraocular tuberculosis, the literature, the experimental work done in this field and his vast clinical material.

The first problem was that of establishing the site of the primary tuberculosis lesion. A careful roentgenographic examination of 300 patients with metastic tuberculosis of the eye showed that in only 15 per cent of the patients was active tuberculosis present in the lungs or in the bronchial glands. However, in many other so-called healthy persons the roentgenographic examination showed old scars in the parenchyma of the lungs and bronchial glands; evidently, the tuberculous process in these patients was of mild form and passed under the disguise of grip or influenza. During such a period the virulent tubercle bacilli might invade the blood stream. The special anatomicophysiologic relation which exists in the uveal tract makes the choroid a favorable site for the hematogenous bacterial influx. Samoilov compares the choroid to a basin, in which the greatly slowed down blood current flowing through the innumerable vascular labyrinths of the choroid favors the settling of the particles of the blood; thus, he explains why the primary intraocular tuberculosis lesion is located invariably in the uveal tract, from which the bacilli may be transmitted to the retina, the sclera or the cornea. This view was also maintained by Aexfeld, Stock and Siegrist.

The tubercle bacilli carried to the uveal tract may be latent for a long time, or they may produce a mild lesion, which also may remain latent for a prolonged period; but when the general and local immunity is weakened, the slightest provocation—mild disease of the eye or trauma—may result in a flare-up of the latent tuberculous lesion in the uvea. The interval between the appearance of the intial latent lesion in the uveal tract, or the presence of the bacilli in the blood stream, and the active process in the uvea may be several years; and this fact explains why it is almost impossible to obtain a culture of tubercle bacilli from the blood in cases of a severe tuberculous lesion in the eye. The lesion in the eye usually does not become activated until the intrathoracic lesion is entirely quiescent, explaining the rarity of simultaneous ocular and pulmonary tuberculosis; only in rare cases of low general immunity are the ocular lesions combined with pulmonary tuberculosis.

The role of the general immunobiologic condition of the organism in the etiology of metastatic tuberculosis of the uvea was shown by the experimental work of Kaminsky and Yusefova in Samoilov's clinic, and the observations of these authors were of aid in the diagnostic problem. If there is an active tuberculous lesion in the lungs with simultaneous severe uveitis, the uveitis could be considered of tuberculous origin only when the Mantoux reaction is negative, i.e., when the general immunity of the organism is greatly lowered. When the Mantoux reaction is positive, the tuberculous character of the uveitis can be eliminated.

The relation of the immunity of the organism and the activation of the ocular metastatic lesions led to the creation of a whole series of reliable, safe diagnostic tests with tuberculin, as well as to a bolder use of tuberculin therapy. If the lesion in the uveal tract is the only tuber-

culous lesion in the organism, large therapeutic doses can be applied, with the expectation of obtaining a localized reaction to each dose, and thus making the therapy effective.

OLGA SITCHEVSKA.

RETINITIS CENTRALIS SEROSA (MASUDA'S DISEASE). S. STENSTROM, Acta ophth. **21**:97, 1944.

The literature concerning this condition is briefly reviewed, and 5 cases of his own are submitted. None of them throws light on the question of etiology, but the author regards it as likely that a circulatory disturbance is the cause of the characteristic macular edema.

O. P. PERKINS.

POLYARTHRITIS URETHRITICA SIMPLEX WITH OCULAR SYMPTOMS (REITER-FREUND SYNDROME). H. SKYDSGAARD, Acta ophth. **21**:107, 1944.

Four cases of the syndrome described by Reiter in 1916 are reported. The syndrome consists in purulent urethritis, purulent conjunctivitis and mutiple swellings of the joints, the exact sequence of involvement being variable.

The etiologic factor is unknown, but it is definitely not gonorrheal.

O. P. PERKINS.

Glaucoma

PRIMARY GLAUCOMA AND THE PITUITARY-DIENCEPHALIC SYSTEM. H. ZONDEK and G. WOLFSOHN, Am. J. Ophth. **30**:569 (May) 1947.

Zondek and Wolfsohn found changes pointing to the pituitary-diencephalic system in 16 out of 22 cases of glaucoma, 6 of these presenting pituitary tumors. They suggest that the term "pituitary-diencephalic" glaucoma be used for such cases.

W. S. REESE.

PATHOGENESIS OF GLAUCOMA. M. MARIN AMAT, Arch. Soc. oftal. hispano-am. **6**:1012 (Oct.) 1946.

After an extensive discussion of the factors and mechanisms involved in the production of primary glaucoma, the author comes to the following conclusions:

1. The ocular hypertension which is the cardinal symptom of glaucoma is the result of an increase in the blood and lymph supply of the eyeball. 2. If this increase takes place suddenly, acute glaucoma occurs; if slowly, chronic glaucoma is the result. 3. The regulatory center for the intraocular circulation is dependent on the neurovegetative system and is represented by the small ganglions located in the ciliary body and in the choroid, which act under the control of the autonomic nervous system. 4. Disturbances in this center produce disturbances in the sympathetic-parasympathetic equilibrium, which regulates the amount of blood flowing in and out of the eyeball. 5. As a consequence of this disturbance of equilibrium dilatation of the blood vessels, stagnation in the circulation, increase in the permeability of the capillary endothelium

and hypertension occur. 6. The causative factor in the alteration of this equilibrium is a primary excitation of the sympathetic nervous system, which brings about an initial and persistent excitation of the parasympathetic nervous system. 7. Therefore, the pathogenesis of glaucoma is predominantly a parasympathetic hypertonic reaction or at times exclusively a parasympathetic action.

On the basis of these statements, Marín Amat draws the following clinical conclusions: 1. The prophylactic treatment of glaucoma should be directed toward avoiding any condition which may bring about excitation of the neurovegetative system, and the "curative" treatment should endeavor to weaken the action of the nerve plexuses in the ciliary body and at the root of the iris. 2. The surgical treatment of glaucoma should be directed against the production of intraocular liquids, and not against their elimination. 3. The existence of nerve ganglions in the root of the iris, in the ciliary body and in the choroid, acting autonomically, explains the failure of the surgical procedures performed on the sympathetic nerve or its ganglions to lower the intraocular tension. It is necessary to act not on the nerves but on the eye—in the root of the iris and in the ciliary body, as here the regulatory center of the intraocular circulation is located.

H. F. Carrasquillo.

Glaucoma—Vascular Necrosis—Expulsive Hemorrhage. W. A. Manschot, Acta ophth. **23**:309, 1945.

An anatomic description is given of 6 eyes in which an expulsive hemorrhage occurred after extraction of the lens. In 5 of these eyes a severe form of glaucoma was present. In 5 of the 6 eyes, necrosis of the posterior ciliary arteries appeared to be the direct cause of the hemorrhage. It is probable that glaucoma can cause vascular necrosis, especially in the posterior ciliary arteries. Further study of a great number of glaucomatous eyes is necessary to confirm this suspicion.

O. P. Perkins.

Hygiene, Sociology, Education and History

Teaching of Ophthalmology in the United States. G. Queiroga, Arq. brasil. de oftal., **8**:75 (June) 1945.

Queiroga, who held a Pan-American Congress of Ophthalmology—Kellogg Foundation fellowship from October 1943 to December 1944, describes the methods of teaching ophthalmology in the United States throughout the medical course. He also gives a short report of his work during the year of his fellowship at the University of Iowa.

M. E. Alvaro.

Injuries

Extensive Traumatic Iridodialysis with Repair. F. W. Newell, Am. J. Ophth. **30**:695 (June) 1947.

Newell reports the case of a 24 year old soldier who sustained a traumatic iridodialysis extending from 10 to 7 o'clock in the left eye

nasally. A successful cosmetic result was obtained by incarcerating shreds of iris in a corneoscleral wound. A brief discussion of this type of surgery is appended.

W. S. REESE.

THE REGENERATION OF WOUNDS OF EXTERNAL MEMBRANE OF THE EYE IN THE LIGHT OF NEW PATHOLOGICO-ANATOMICAL RESULTS. E. T. LEVKOIEVA, Brit. J. Ophth. **31**:336 (June) 1947.

The subject is considered under the following heads: clinical and anatomic approach to perforating wounds of the eye; a review of the methods of closing ocular wounds; the regenerative process of the external membranes of the eye, and classification of eye injuries.

Levkoieva reaches the following conclusions: The regeneration of the sclera and cornea is not the ordinary granulation process of connective tissue, proceeding by the fibrovascular way, with its peculiar cycle of development of the cellular elements, but a proliferation *sui generis* of similar cellular forms that morphologically are near to tissue cultures. The dynamics of this process are characterized by an extraordinary intensity, as a result of which—in unfavorable conditions—is seen a surplus growth, chiefly as a result of the penetration of the regenerative tissue in the liquid milieux of the eye.

Following the described peculiarities of this process and the idea that the eye, as a closed chamber, is ideally adapted for tissue cultures in vitro, one should use the experience of histologists and their ability to regulate the growth of the tissue elements.

Clinical and experimental research of the best methods of closure of wounds of the eye should be undertaken and also of the regulation of the regenerative process of the healing of the wound; besides seeking surgical perfection, one should treat this procedure as analogous to tissue culture.

In connection with surplus regeneration of the wound of the eye is seen an autonomous fibromatosis in the eye, pathologically a different form of disease, that has nothing in common with sympathetic ophthalmia, but is clinically similar to it. With present knowledge, it is still included under the common diagnosis of traumatic iridocyclitis. It should be differentiated from this disease in the future.

W. ZENTMAYER.

Lens

ENDOCRINE CATARACT: REPORT OF CASES. M. L. GUILLAUMAT, Bull. Soc. d'opht. de Paris, (Nov.-Dec.) 1946, p. 86.

Guillaumat describes 5 patients with cataract which he believes is of endocrine origin. He bases his classification on the facts that the age at which such cataract occurs is usually between 40 and 50; that the lesion is under the posterior capsule; that arterial tension is normal or below; that contractures occur in these patients similar to those found in patients with tetany, and that eighth nerve impairment is present. A study of the family tree reveals antecedents with cataracts. The calcium content of the blood is rarely modified. Finally, by using parathyroid

hormone with vitamin D and calcium, only 1 of the 5 patients gave any sign that therapy was of value.

L. L. MAYER.

Neurology

HYPERTONIC PARALYSIS OF GAZE. J. DEREUX, Ann. d'ocul. **178**:199 (May) 1945.

The author reports 2 cases of chronic (Huntington's) chorea associated with paralysis of all voluntary ocular movements. The first case, that of a woman aged 32, was characterized by all the neurologic signs and symptoms of progressive chorea. The eyes could not voluntarily be moved in any direction. Following movements were likewise absent. Convergence was accomplished with difficulty. When the patient was told to look to the right, the eyes remained immobile, but she turned her head to the right. Once the head was turned, further conjugate movement to the right was possible. If the head was fixed so that it could not be turned to the right, the eyes remained immobile.

There was no other evidence of nuclear paralysis. The results of ocular examination were otherwise normal. After the injection of 0.25 mg. of scopolamine hydrobromide, her gait became freer, and voluntary conjugate ocular movements were present in all directions. The second case was exactly similar, but the patient did not receive an injection of scopolamine.

The author states that he knows of no other reported cases that are exactly like his. The loss of voluntary movement with preservation of reflex movements is unusual. The ocular movements that were carried out, i.e., the conjugate movements possible when the head was turned to one side, were slow and jerky, as though the eyes had to overcome some resistance. Alajouanine was the first to describe a somewhat similar condition, and he expressed the belief that the condition was caused by hypertonicity of the muscles. Schaeffer took exception to this interpretation, since the Parkinson syndrome is due to a lesion of the extrapyramidal tract and is characterized by preservation of voluntary movements but loss of automatic movements. Unless the ocular muscles are an exception to this, he does not see how the findings can be explained on the basis of muscle tonus. Pierre von Morax stated that the syndrome of hypertonicity might be a modification of voluntary paralysis of gaze. He mentioned the negative response to scopolamine in Alajouanine's case.

The author concludes that there are two types of paralysis of gaze, the true paralysis and the hypertonic paralysis. He bases this statement on three presumptive signs: (1) the slowness of the ocular movements, (2) the accompanying signs of a lesion of the extrapyramidal tract and (3) the possible occurrence of the voluntary paralysis in all directions of gaze. The unequivocal sign is the disappearance of the paralysis following the injection of scopolamine.

P. ROBB MCDONALD, M. D.

Ocular Muscles

DUANE'S SYNDROME. J. SERPA, Rev. brasil. oftal. **4**:43 (Sept.) 1945.

A case of Duane's syndrome is reported in detail. Serpa places Duane's syndrome with Austregesilo Filho's neurodysplasia (1943), a "generic designation of an alteration in the embryogenesis of the nervous system, encephalic or medullary."

M. E. ALVARO.

SQUINTING POSITION OF WEAK-SIGHTED EYES. P. BROENDSTRUP, Acta ophth. **22**:386, 1944.

The author has examined the nature of the ocular deviation assumed by the weak eye in a series of 162 persons affected with monocular cataract or aphakia. The patients are divided into three groups: Group 1 comprised 32 cases in which the cataract was congenital. Here divergence was found in 50 per cent and convergence in 40 per cent. Group 2 comprised 70 cases in which the cataract was acquired before the tenth year of life. Here divergence was found in 74 per cent and convergence in 13 per cent. Group 3 comprised 60 cases in which the eye became affected at the age of 11 or later. Here divergence was found in 67 per cent and convergence in 12 per cent.

O. P. PERKINS.

Operations

REPAIR OF FACIAL DEFECTS BY LOW-NECK PEDICLE FLAPS. ROBERT H. IVY, Plastic & Reconstruc. Surg. **1**:117, 1946.

Cutaneous and subcutaneous tissue from the lower part of the neck is devoid of hair and is similar to that of the face in texture and color. The scar from its removal is usually inconspicuous and can be readily concealed. Pedicles from the neck may safely cross the midline, which refutes the dictum that a pedicle should never cross that line. Jerome Webster, T. G. Blocker and the author have had good results with pedicles from the lower part of the neck. Convincing photographs support these successes.

L. P. GUY.

MULTIPLE EXCISION AND Z PLASTICS IN SURFACE RECONSTRUCTION. FERRIS SMITH, Plastic & Reconstruc. Surg. **1**:170, 1946.

A new use of the Z plastic procedure combined with multiple excision of undesirable tissue is emphasized as the method of choice for restoring to normal deformities caused by burns, keloids, scars and congenital lesions but not if the tissue is malignant. This method reduces consequent distortion of the eyelids, nose and angle of the mouth and ears. A more desirable cosmetic result is obtained than with transplanted skin flaps and grafts. The method is not useful in the upper infraorbital area of the male because of the introduction of hair-bearing skin.

L. P. GUY.

Orbit, Eyeball and Accessory Sinuses

UNILATERAL EXOPHTHALMOS, AN EARLY SIGN IN THYROTOXICOSIS. W. H. KISNER and H. MAHORNER, Surg., Gynec. & Obst. **84**:326 (March) 1947.

Kisner and Mahorner report 5 cases of unilateral exophthalmos due to toxic diffuse goiter. In all of these cases the unilateral exophthalmos was a prominent sign, and in some it was the only one noticed by the patient. The cause of exophthalmos is not established, but from experimental studies it would appear that a factor in the secretion from the anterior lobe of the pituitary has the property of producing exophthalmos, and the same or a different factor has the property of inducing hyperplasia of the thyroid gland. The erroneous impression exists that the exophthalmos immediately subsides following thyroidectomy, but even in cases with high basal metabolic rates the exophthalmos is frequently a little worse in the weeks immediately after the operation. Only after many weeks and months does the exophthalmos gradually subside. Because of the long time over which improvement in exophthalmos after thyroidectomy may occur, radical procedures, such as the Naffziger operation, should be deferred unless extreme proptosis greatly jeopardizes the sight of the eye.

J.A.M.A., W. ZENTMAYER.

PANOPHTHALMITIS IN A PREMATURE INFANT TREATED BY STREPTOMYCIN. L. B. SOMERVILLE-LARGE, Brit. J. Ophth. **31**:362 (June) 1947.

A case of panophthalmitis in a premature child following infection of the umbilical cord by Bacillus proteus is described. The initial treatment consisted in the administration of sulfadiazine by mouth and penicillin by injection. During the first six days of this treatment the ocular condition became steadily worse. Streptomycin was then substituted, and although the lid and orbital condition improved, on the ninth day of the beginning of this treatment the globe perforated and evisceration was performed. The author considers the streptomycin to have overcome the inflammation of the uveal tissue, as prior to the commencement of treatment with streptomycin B. proteus was found in pure culture in the anterior chamber, but after treatment the cultures from the highly infected globe were negative.

W. ZENTMAYER.

Physiology

RATE OF DARK ADAPTATION AND REGIONAL THRESHOLD GRADIENT OF THE DARK-ADAPTED EYE: PHYSIOLOGIC AND CLINICAL STUDIES. L. L. SLOAN, Am. J. Ophth. **30**:705 (June) 1947.

Sloan studied 9 patients, in addition to normal persons, whose elevated light thresholds were restored to normal by vitamin therapy. The findings indicate that riboflavin, in addition to vitamin A, may be required to effect complete recovery. These studies suggest that concentric contraction of the visual field occurs frequently in patients with ocular vitamin A deficiency and probably indicates cone as well as rod involvement.

W. S. REESE.

THE NUMBER OF QUANTUMS NECESSARY FOR THE PERCEPTION OF LIGHT BY THE HUMAN EYE. H. A. VAN DER VELDEN, Ophthalmologia **111**:321 (June) 1946.

The author criticizes previous work done on the influence of the quantum character of light on vision at low levels of illumination. He considers that too little emphasis has ben placed on the statistical character of the light quanta when determining the number of quanta necessary for a light stimulus. A method is described for the determination of the number of absorbed quanta in the visual purple necessary for the perception of light under conditions of dim illumination. An analysis is then made of the statistics on the observation of light flashes, and the theoretic relationships and the experimental data were compared. Assuming that k light quanta are necessary for the perception of light, the author found that two such quanta fit all the experimental curves. He considers that it is probable that the cooperation between the two quanta takes place in the nervous system, a concept which is in accordance with other concepts in neurophysiology.

F. H. ADLER.

Refraction and Accommodation

CONTACT LENSES IN EXCELSIS. A. H. BRIGGS, Brit. J. Ophth. **31**:304 (May) 1947.

A man aged 22 had been rejected for service in the Civil Air Guard because of myopia. Contact lenses were successfully fitted, and he was then passed without their presence being suspected. The lenses were not detected at two subsequent medical board examinations, in America and on his return to England. He served in the bomber squadron over Germany. Subsequently, he served as a captain of transport aircraft. He entered the service in 1940 and was discharged Jan. 1, 1947. He was decorated for courage, determination and devotion to duty. Briggs suggests that the visual acuity regulations for the service ought to be revised to show to what extent contact lenses will be permitted. He asks how far it is justifiable to aid and abet a patient in procuring contact lenses, knowing they are likely to be used to defraud a medical examiner, and how far such a subterfuge is unfair.

W. ZENTMAYER.

FUKALA OPERATION FOR HIGH MYOPIA. C. PESCATORI, Rassegna ital. d'ottal. **13**:49, 1946.

The author reports on some cases of high myopia in which the clear lens was extracted. The method of operation consisted of a discission with secondary suction of the opaque lens. No complication except 1 case of glaucoma was met. The only disadvantage is the necessity of repeating the operation when suction of the lens substance is not complete. The improvement of visual acuity is constant. The preferable time for intervention is between the ages of 8 and 20. The grade of myopia best suited is about 20 D. The postoperative astigmatism amounted to 2 D. Changes in the fundus do not constitute a real contraindication, as long as they do not reduce the vision to less than 20/200.

G. B. BIETTI—J. J. LOPRESTI.

Retina and Optic Nerve

RECENT OBSERVATIONS ON THE PATHOGENESIS OF DIABETIC RETINOSIS. F. NASTRI, Boll. d'Ocul. **19**:24, 1945.

Investigations were directed primarily toward showing the behavior of the lipids, vitamin K, vitamin A, carotene and prothrombin in the blood of diabetic persons presenting retinal lesions.

The results obtained revealed that in patients with diabetic retinosis there was a definite increase in the blood lipids, hypervitaminosis A and K and an increase of carotene, as well as a relative reduction in prothrombin.

The author interprets these findings as an expression of altered hepatic function in patients presenting the picture of diabetic retinosis.

G. BIETTI—J. J. LO-PRESTI.

PRELIMINARY ATTEMPTS AT THE SURGICAL TREATMENT OF COATS'S DISEASE. A RUBINO, Riv. di oftal. **1**:285, 1946.

On the assumption that the primary cause of Coats's disease resides in vascular changes in the choroid, the author treated 2 patients with diathermy coagulation of the choroid through the sclera, with the idea of obliterating and coagulating vessels and arresting the changes occurring in their walls, much as increased permeability and ectasia. The procedure is completed with one or more perforating punctures to permit escape of the subretinal fluid. The results obtained are promising.

G. B. BIETTI—J. J. LO-PRESTI.

RETINAL DETACHMENT, PREGNANCY AND ECTOPIA LENTIS. V. VENTOLA and F. IRIBARREN, Arch. oftal. de Buenos Aires **21**:232 (Aug.) 1946.

The patient came to the authors in the sixth month of pregnancy. Ten days before the examination sudden decrease of vision was noted in the right eye. Vision was equal to perception of hand movements. There was congenital bilateral ectopia lentis. The retina of the left eye was normal, no signs of retinitis gravidarum being noted. In the right eye a slightly elevated retinal detachment in the temporal area was observed, no tear being visible. Two problems then had to be solved: the possible relation between the retinal detachment and the pregnancy, and the advisability of operation. As retinal detachment is a frequent complication of ectopia lentis and the prognosis is not very good, and as further examinations showed no tear, rest in bed and a nontoxic diet were ordered. If, about a month after the confinement, a cure has not been effected, an operation will be performed.

M. E. ALVARO.

RETINAL EDEMA IN TUBERCULOUS DISEASE OF THE ANTERIOR SEGMENT OF THE EYE. A. SAMOILOV, Vestnik oftal. **26**:20, 1946.

The anterior segment of the eye is frequently involved in metastatic tuberculosis of the eye. The precipitates on Descemet's membrane and opacities of the vitreous in tuberculosis of the uveal tract, however, do

not correspond to the frequently observed marked decrease of visual acuity. Samoilov believes that the tuberculous process spreads from the anterior parts of the eye to the posterior segment of the uveal tract and causes an edema of the retina and this explains the reduction of vision at the moment of activation of the tuberculous lesion in the anterior segment of the uveal tract. The enlargement of the blindspot, when examined with the campimeter, confirms the fact that edema of the retina is present.

Samoilov experimented on an eye with sarcoma of the choroid in the following manner: Campimetry revealed no enlargement of the blindspot; the vision in the quiet eye was 20/20. A paracentesis was done, and 0.4 cc. of the aqueous was withdrawn. The eye became inflamed (ciliary infection), and the campimeter showed a scotoma two hours after the puncture of the anterior chamber. Twenty-seven hours after the slight trauma the eye, which was quiet again, was enucleated. Pathologic examination did not reveal edema of the retina or changes in the choroid, except the sarcoma and a small detachment of the retina adjacent to the site of the tumor of the choroid. This transitory edema of the retina in response to the irritation of the iris and ciliary body, produced by slight trauma, without involvement of the choroid, indicates that retinal edema regularly appears in an active process of the anterior segment of the eye.

In a number of cases of anterior uveitis examination by the campimeter invariably revealed an enlargement of the blindspot, particularly if there was a responsive reaction to treatment with tuberculin. Case histories illustrate the point of the author.

Samoilov comes to the following conclusions:

The most sensitive tuberculin-campimetric test can be used not only for choroiditis but also when there is any other localization of the tuberculous lesion in the eye.

The decrease of vision observed in isolated severe tuberculous uveitis is caused by retinal edema as a reaction to the inflammatory process in the anterior segment of the eye.

The use of calcium iontophoresis in tuberculosis of the uvea acts not only as a desensitizing factor but also as a valuable therapeutic agent by decreasing the retinal edema and thus increasing the visual function.

Further observations will show whether the retinal edema appears specifically in tuberculous lesions of the eye or whether it can be present in lesions of the eye with different cause.

OLGA SITCHEVSKA.

INVESTIGATIONS ON THE INFLUENCE OF K AVITAMINOSIS ON THE OCCURRENCE OF RETINAL HEMORRHAGES IN THE NEWBORN. H. WILLE, Acta aphth. **22**:261, 1944.

In a control series of 594 newborn infants, the incidence of retinal hemorrhage was 42.4 per cent. In the children of mothers who had received intramuscular injections of a preparation of vitamin K at the commencement of labor, the incidence of retinal hemorrhage was reduced to 32.9 per cent.

O. P. PERKINS.

Trachoma

CONTEMPORARY STATE OF TREATMENT OF TRACHOMA. A. MURZIN, Vestnik oftal. **26**:25, 1947.

A review of the literature on the etiology and treatment of trachoma and the clinical experience of the Kazan experimental trachomatous institute are given. The enthusiasm of the ophthalmologists for the Noguchi gram-negative bacillus and the rickettsia as the etiologic factors of trachoma has abated, and the role of the Prowazek-Halberstädter bodies as the cause of trachoma is being reconsidered.

Scrofulosis, tuberculosis, syphilis, avitaminosis and allergy have an important bearing on the course of the trachomatous process and on the local treatment. Trachoma is a chronic proliferative inflammation, and the treatment must conform to the various clinical stages of the disease.

The mechanical therapeutic measures are widely used in the United Soviet Socialist Republics in the form of repeated expressions of the follicles with local treatment of the conjunctiva in the intervals. The expression acts not only as a mechanical but also as a stimulating or irritating factor, by mobilizing the cellular elements for the control of the infection. Expression therapy is most effective in trachoma in the first and second stages or the granular stage of the disease, and is applied frequently in young adults and children. However, it is contraindicated in cases with a secondary infection of the conjunctival sac, and in allergic irritation of the conjunctiva, as it may cause an exacerbation of the process and cause a corneal ulcer.

The experience of the Kazan Institute is that sulfonamide therapy, both local and general, is of positive value, mainly in corneal involvement and in secondary conjunctival infection. The action of the sulfonamide compounds on the trachomatous changes is rather slow, although it causes a gradual absorption of the infiltrates and follicles. Murzin, therefore, considers it advisable to combine sulfonamide therapy with expressions of the follicles. The sulfonamide compounds are most effective in the first and second stages of trachoma. A study is being made of the combined treatment of trachoma with sulfonamide compounds, taken orally, and autohematotherapy.

The newer antibiotics—penicillin, gramicidin and aspergillin—act most effectively in secondary infections in trachoma.

In children the local application of sulfonamide compounds gives best results.

Diathermocoagulation has been used in the Kazan Institute since 1941 in cases of resistant, long-standing trachoma, in 3 of which the disease did not respond to routine treatment. In 53 cases, the third therapeutic stage of trachoma was changed into the fourth stage within twenty-two to thirty-two days.

Tissue therapy after Filatov's method has not influenced the course of trachoma.

OLGA SITCHEVSKA.

SOCIETY TRANSACTIONS

Edited by Dr. W. L. Benedict

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

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Sixteenth Annual Meeting, San Francisco, July 2, 1946.

Cytologic Character of Conjunctival Exudates. Dr. Phillips Thygeson, San Jose, Calif.

In a microscopic study of smears of exudate and conjunctival scrapings in 2,000 cases of conjunctivitis of diverse origin, variations in leukocytic reactions and epithelial changes were observed to be sufficiently pronounced to have diagnostic value.

Polymorphonuclear cell exudates were characteristic of bacterial infections in general, but there were a few exceptions. Morax-Axenfeld conjunctivitis was characterized by a fibrinous exudate without leukocytes unless there was a secondary staphylococcic infection. Chronic conjunctivitis due to Neisseria catarrhalis also showed a minimal or no leukocytic reaction.

Conjunctivitis produced by the typical viruses always showed a characteristic mononuclear cell exudate with few, if any, polymorphonuclear cells. In contrast, the three viruses of the psittacosis-lymphogranuloma venereum group of viruses, those of trachoma, inclusion blennorrhea and lymphogranuloma venereum, always showed a polymorphonuclear cell exudate.

Epithelial changes consisting of various degrees of keratinization were of value in the diagnosis of early vitamin A deficiency. Mild keratinization of the epithelium combined with an increase in goblet cells and mucus was characteristic of keratoconjunctivitis sicca.

A predominance of eosinophils in the exudate was characteristic of vernal conjunctivitis and of typical conjunctival allergies, such as conjunctivitis associated with hay fever. With bacterial allergy, as exemplified by phlyctenular conjunctivitis, eosinophils were not present in the exudate. A conjunctival basophilia was also observed with the typical allergies but was neither so constant nor so specific as the eosinophilia. The occurrence of free eosinophilic and basophilic granules released from disintegrating cells was found to have diagnostic value.

The expressed follicular contents of the cells of trachoma and that of other follicular conjunctivitides showed striking differences in cytologic character. These differences appeared to be related to the cellular necrosis which is a striking feature of trachoma but not of the other diseases.

In only a few exceptional instances were the cytologic changes observed in this study pathognomonic of the etiologic type of conjunctivitis concerned, but when correlated with clinical and bacteriologic findings they were often of diagnostic importance.

DISCUSSION

DR. JAMES H. ALLEN, Iowa City: Can a distinction be made between acute conjunctivitis, Beal type, and epidemic keratoconjunctivitis on the basis of cytologic differences?

DR. PHILLIPS THYGESON, San Jose, Calif.: I think that no distinction can be made at present between the cytologic changes in these two diseases. It was thought at one time that specific inclusion bodies were associated with epidemic conjunctivitis, that is, bluish, amorphous bodies in the cytoplasm of conjunctival and epithelial cells of the cornea which had some diagnostic significance, but these same bodies have since been observed with other diseases, and it is thought that they are nonspecific.

DR. JAMES H. ALLEN, Iowa City: Do you consider macrophages (Leber cells) pathognomonic of trachoma?

DR. PHILLIPS THYGESON, San Jose, Calif.: The Leber cell is nothing but a large macrophage. Such cells were observed with trachoma and were certainly more numerous than with any other type of conjunctivitis studied, but they were also noted with other infections. It seems to me that the presence of numerous Leber cells in association with signs of cell necrosis and a predominance of lymphoblasts does indeed make a pathognomonic picture. I believe that macrophages in other types of conjunctivitis tend to be definitely smaller than the Leber cell, which is an extraordinarily large macrophage.

I am sure that the cells stem from the same source, but there is an extraordinary difference in size between macrophages in cases of trachoma and those associated with other types of conjunctivitis.

DR. JAMES H. ALLEN, Iowa City: Will you discuss the importance of a proper selection of the site for removal of material for cytologic study?

DR. PHILLIPS THYGESON, San Jose, Calif.: It is a good rule to take cytologic material from the point of maximum intensity of the disease. In cases in which smears of exudate are taken, this is not of much significance, since most exudate accumulates in the inner canthus. Scrapings, however, are best taken from the site of maximum intensity of the disease.

When one is looking for evidence of suspected vitamin A deficiency, it is important to recognize that the temporal portion of the limbus is the site most commonly affected in the early stages. One should, then, take scrapings from the area of the outer temporal portion of the limbus. This is the site where a Bitot spot is most commonly seen.

DR. DONALD J. LYLE, Cincinnati: What are the best stains to use routinely in the laboratory investigation?

DR. PHILLIPS THYGESON, San Jose, Calif.: I have used a half-dozen cytologic stains, and I prefer the Giemsa stain. The material is fixed in absolute methyl alcohol and then stained in dilute Giemsa so-

lution (1 drop to 2 cc. of neutral distilled water) for about an hour. The slide is then passed through two changes of 95 per cent alcohol to remove the debris of the stain. This method results in a very satisfactory cytologic stain. Then, there is the Wright stain, which is satisfactory and is more rapid. I am sure there are two or three other stains which would work equally well, but I, personally, prefer the Giemsa stain.

DR. V. C. RAMBO, Mungeli, Central Provinces, India: Will Dr. Thygeson discuss the differentiation of inclusion blennorrhea and trachoma?

DR. PHILLIPS THYGESON, San Jose, Calif.: I think it is possible to make a cytologic differentiation between these two diseases, especially in the adult. Both diseases have identical inclusion bodies; both diseases are characterized by a polymorphonuclear cell exudate. It is the cytologic picture of the follicles which makes the differentiation possible. In inclusion conjunctivitis in the adult, the follicles show none of the degenerative changes characteristic of trachoma, and one gets the cytologic picture of the nontrachomatous follicle, in contrast to the numerous cytologic changes so characteristic of trachoma.

I recognize that clinical differentiation is possible in most cases, but there are certainly occasional confusing cases in which cytologic study may be of value.

DR. K. W. ASCHER, Cincinnati: Did you observe, in cases of vitamin A deficiency, syncytium-like membranes of keratinized epithelial cells?

DR. PHILLIPS THYGESON, San Jose, Calif.: I may have seen such changes, but I did not recognize them as particularly characteristic. I am sorry; I really cannot answer that question.

DR. EDWARD C. ELLETT, Memphis, Tenn.: In speaking of the reaction to atropine, Dr. Thygeson made the distinction that the reaction to atropine was an allergic one and that to physostigmine a toxic one. Did he make any tests for sensitivity to these two drugs on patients with these conditions?

DR. PHILLIPS THYGESON, San Jose, Calif.: First, I noted that there was a striking clinical difference between the types of conjunctivitis produced by these two drugs. The reaction to atropine was typically a contact conjunctivitis and dermatitis, with widespread dermatitis of the eyelids, whereas I never saw cutaneous reactions produced by physostigmine. I recognize that they may well occur, but I have not seen them personally. Second, I noted that the conjunctival reaction in atropine conjunctivitis was a papillary hypertrophy, whereas in physostigmine conjunctivitis it was a follicular hypertrophy.

I made a number of tests, both patch and intradermal, and I was consistently able to obtain a positive reaction to the patch test for atropine. Some were low grade and others rather violent. However, I never succeeded in obtaining a reaction to the patch test for physostigmine. I did not make serologic studies.

Macular Edema. DR. ARTHUR J. BEDELL, Albany, N. Y.

The common causes of edema of the macular region were demonstrated.

Special attention was drawn to Berlin's edema, the various causes of holes at the macula and the inflammatory reactions of retinochoroiditis and retinitis.

Since in hemorrhagic exudate and traumatic hole it is probable that there is always edema at some time, cases of each were included.

Preretinal and retinal edema were explained as a pushing outward of the vitreous, producing the ring-shaped light reflex which is on it.

Some of the recent papers on macular edema were referred to, and additional illustrations of juvenile macular degeneration, central serous retinopathy, local detachment of the retina and foveomacular diseases were presented.

Conclusions.—Edema of the macular region may be the isolated expression of either a local or a general tissue reaction. The edema may be limited to and disappear from the macula, or it may be the precursor of extensive retinochoroiditis or a gross macular change. The healed macula may show pigmented specks, white dots, heaped-up pigment, atrophy or thick scars, which may be smooth and flat or rough and nodular.

This paper was illustrated by a series of "kodachrome" photographs.

Experimental Dinitrophenol Cataract. DR. J. W. BETTMAN, San Francisco.

Dinitrophenol was estimated by Horner to be associated with the development of cataract in obese persons in an incidence of 0.86 per cent. It was associated with the development of cataract in obese mice in an incidence of 7.5 per cent. The cataract has often occurred in human subjects after the withdrawal of dinitrophenol therapy; it did not occur in obese mice after the withdrawal of dinitrophenol. It did not occur in ordinary, nonobese mice in any circumstances.

Dinitrophenol caused lenticular opacities in fowl within eight hours after a diet containing dinitrophenol was instituted. The opacities cleared spontaneously while the fowl were still on the diet. In comparable doses, dinitrophenol failed to cause opacities of the lens in young or adult obese mice whether or not they were subjected to higher temperatures.

The direct injection of dinitrophenol into the anterior chamber of chickens and rabbits caused lenticular opacities in each species within approximately one-half hour. The opacities cleared within twenty-four hours. Rabbits did not acquire opacities of the lens when fed dinitrophenol. The direct immersion of the lenses of chickens, obese mice and rabbits into a solution of dinitrophenol did not produce opacity in a comparable length of time

Conclusions.—The results of these experiments led to the following conclusions and conjectures:

1. Dinitrophenol acts only on the lens *in vivo* of mammalian and avian species.

2. The lens *in vitro* does not show this opacity. This may be due to one of several factors: *(a)* Dinitrophenol, when in the anterior chamber, forms another compound, which then acts on the lens. *(b)* The permeability of the lens capsule is different when the lens is *in vitro*

than when it is in its normal state. *(c)* Dinitrophenal interferes with a phase of metabolism of the living lens, such as production of an increased need for oxygen or the formation of more lactic acid.

3. The failure of the transient opacities observed in fowl to develop in mammals is due to a difference in metabolism of the species, and not to a difference in the lenses themselves.

4. The significance of differences in metabolism is confirmed by the occasional occurrence of permanent cataracts in congenitally obese mice. Such opacities did not occur in nonobese mice. This frequency of cataract formation is comparable to the incidence of cataract in obese persons and may explain the previous failures of numerous investigations to produce cataract in experimental mammals.

5. The difference in incidence of cataract in fowl and in mammals is apparently not due to the differenee in body temperature. The age of the animal is little, if at all, related.

Numerous questions related to dinitrophenol cataract remain unanswered. Is the cataract-producing action of dinitrophenol due to its effect on oxidation or on sugar metabolism or to something else? Why does the cataract which develops so rapidly in a chick clear spontaneously while the chick is still receiving the same concentration of dinitrophenol? Why did cataract occur with great rapidity in human subjects months after the ingestion of dinitrophenol had been discontinued?

Work is being continued in an attempt to answer some of these vexing problems.

DISCUSSION

DR. CLYDE A. CLAPP, Baltimore: I should like to ask in how many of the male subjects dinitrophenol cataract developed. Are there any reports in the literature?

What was the difference as seen with the slit lamp between the co-called reversible opacities in the birds and the permanent opacities in the mice?

DR. J. W. BETTMAN, San Francisco: Dinitrophenol cataract has been reported in human male subjects in 1 or 2 instances. I have forgotten the precise number of cases in the literature. They are not common, but they have been reported.

The picture of the reversible cataract in the chick seen with the slit lamp was that of a dense opacity entirely limited to the subcapsular layers of the lens. The remainder of the lens was not involved at any stage.

In the permanent opacities in the mice, the first observable change was the same type of subcapsular opacity, posterior at first and then anterior; in association with the development of the anterior opacity, or at about that stage, the nucleus begins to get a bit milky, and an opacity then develops in the entire lens.

DR. CONRAD BERENS, New York: Are dinitrophenol and dinitrocresol synonymous terms? A clinician in New York claimed that there is a difference, but in 2 obese women who were treated with dinitrocresol 'cataracts developed rapidly. One was 28 and the other 60 years of age.

DR. J. W. BETTMAN, San Francisco: The terms dinitrophenol and dinitrocresol are not synonymous, but the drugs act, so far is is known, in precisely the same manner. Clinically, dinitrophenol has been used

largely in the United States, and dinitrocresol in Europe. They both produce cataract, and so far as I know, they both act in the same manner. The group of drugs to which they belong is usually designated as the "dinitro bodies," because the substances are so similar in their action.

Changes in the Angioscotomas Associated with the Oral Administration of Hexobarbital Soluble. DR. AUSTIN I. FINK.

For some time ophthalmologists have been concerned with the question whether barbiturates are contraindicated in treatment of patients with glaucoma. This concern has derived to a great extent from the observation that large doses of barbiturates have produced dilatation and have increased the permeability of the cerebral blood vessels and the capillary bed.

Angioscotometry was chosen as a suitable method for this experiment, since changes in the normal angioscotoma are assumed to represent alterations in the function of the retinal perivascular space.

The scotoma was mapped according to the method advocated by Evans. The defects in the visual fields could thus be studied both qualitatively and quantitatively.

Studies were carried out on 10 subjects, 9 women and 1 man. The ages of the subjects ranged from 21 to 26 years. All known causes of alteration of the angioscotoma were carefully eliminated. Each subject was in good health.

On a controlled series of 5 of the subjects an experiment was carried out in which capsules containing 4 grains of lactose (0.26 Gm.) were administered orally. The subjects did not know that the capsules contained merely a placebo. The purpose of the control study was to ascertain whether a psychologic factor was present and was a factor in causing the alterations in the angioscotomas occurring after the ingestion of hexobarbital sodium. The method, technic and procedure employed were identical with those used for the studies of hexobarbital. The results demonstrated that in the series of 5 subjects no alteration in the angioscotoma was recognizable.

The oral administration of 4 grains (0.26 Gm.) of hexobarbital sodium was associated with widening of the angioscotoma in 8 of 10 subjects. In the other 2 subjects no recognizable change was shown.

Administration of a placebo containing 4 grains of lactose to 5 of the subjects of the hexobarbital series produced no alteration in the angioscotoma.

One might ascribe the associated effect of hexobarbital sodium on the normal angioscotoma to changes in *(a)* the functions of retinal perivascular space, *(b)* conductivity of the retinal neurons and synaptic junctions and *(c)* the parasympathetic nervous system.

Relation of Maternal Vitamin A Intake, Level of Vitamin A in the Maternal Blood and Ocular Abnormalities in the Offspring of the Rat. DR. BLANCHE JACKSON and DR. V. EVERETT KINSEY, Boston.

In accordance with technics devised by Warkany and Schraffenberger, a series of 57 weanling female rats were grown to maturity

without the accumulation of hepatic stores of vitamin A. They were then bred and given only minimal amounts of vitamin A during pregnancy. Four of the mothers carried their festuses to advanced stages of development. The eyes of the young in these litters showed the abnormalities which have been described by Warkany and Schraffenberger.

To determine the limiting level of the dose of vitamin A for female rats producing young with abnormal eyes, similarly prepared female rats were given 2, 3, 5 or 10 U.S.P. units of vitamin A daily. They were then bred, and the supplementary administration of the vitamin was continued at the same level. Young obtained from mothers fed less than 3 to 5 U.S.P. units daily showed the ocular defects already mentioned, whereas all those receiving more than this amount of the vitamin had normal eyes, even though in many cases the dose of vitamin A was insufficient for normal delivery.

Values for vitamin A of the serum taken during pregnancy from female rats producing young with abnormal eyes were found to be less than 12 U.S.P. units per hundred cubic centimeters in every instance (normal, 75 U.S.P. units per hundred cubic centimeters). The addition of 100 U.S.P. units of vitamin A daily or the feeding of a stock ration after the fifteenth day of pregnancy, with or without treatment with penicillin or sulfathiazole, did not reduce the high percentage of fetal resorption observed in the pervious experiments.

It is concluded that ocular defects occur in the young rat only when the maternal vitamin A deficiency is extremely severe, so advanced, in fact, that fetal resorption is common and normal birth is impossible.

To the extent that the physiologic processes associated with reproduction in human beings parallel those in the rat, it may be inferred that vitamin A defiiciency in the mother is not a probable cause of retrolental fibroplasia.

DISCUSSION

DR. CONRAD BERENS, New York: This study is a piece of research which is vital to the prevention of blindness. About 51 per cent of blindness in the schools for the blind is due to congenital abnormalities.

DR. DERRICK VAIL, Chicago: Were any skeletal malformations observed, especially in the optic foramen or at the base of the skull?

DR. V. EVERETT KINSEY, Boston: We have not yet examined the eyes of the animals for other defects, including skeletal abnormalities; so I am unable to answer that question. Warkany, I believe, has described such defects in detail.

DR. DERRICK VAIL, Chicago: I wish to sound a note of warning here. A few weeks ago, I testified in a criminal court case brought against a specialist in quack vitamin therapy who cited experimental work, reported in Iowa, on vitamin D deficiency as a cause of anophthalmos in a litter of newborn pigs. In his pamphlets, broadcast widely to the public, he used the reports of these experiments to terrify pregnant women and urged them to buy his vitamin product as a prevention of blindness in the unborn child.

I should like to have a firm statement to the effect that the results of your experiments are not yet applicable to human beings.

DR. V. EVERETT KINSEY, Boston: I think our conclusion was to the effect that, in so far as the physiologic processes were the same in rats and in human beings, vitamin A deficiency is not a probable cause of retrolental fibroplasia.

Even though we have to change our minds, I think that, for the record, it might be well to be overcautious and to say definitely that these results do not suggest that maternal vitamin A deficiency is in any way associated with ocular abnormalities in infants.

DR. T. L. TERRY, Boston: It is not intended to detract from this presentation, but I think it would interest you to know that pediatricians working on the problem of retrolental fibroplasia found clinically that this abnormality, which Jackson and Kinsey have reproduced, has developed in 2 infants whose vitamin A in the blood level was kept normal by therapeutic measures. It may interest you further that, according to Clifford and Allers, vitamin A, when dissolved in oil, is not absorbed by the premature infant from the gastrointestinal tract, nor is it absorbed after subcutaneous or intramuscular injection. These authors found that when the vitamin A is dissolved in glycerol instead of oil the level of the vitamin in the blood was elevated. In 2 infants who had received such injections, retrolental fibroplasia developed despite normal vitamin A levels in the blood.

Role of the Lens Substance in Experimental Gonorrheal Iritis.

DR. MAURICE J. DRELL, MISS MARJORIE BOHNHOFF and DR. C. PHILLIP MILLER, Chicago.

In the course of studies on experimental gonorrheal iritis in rabbits, it was noted that the infection was serever and more likely to become chronic in eyes in which the lens had been traumatized at the time of inoculation. The present study was undertaken in an effort to explain this observation and to evaluate the role played by the lens substance in the experimental infection.

The inoculation of gonococci into the anterior chamber of the rabbit with injury to the lens resulted in a moderately severe and chronic inflammatory reaction. The inoculation of gonococci without injury to the lens produced a mild inflammatory reaction. Inoculation of a gonococcus-lens mixture without injury to the lens usually caused a similar reaction. The injection of lens substance without injury to the lens or the injection of isotonic solution of sodium chloride with injury to the lens produced only an insignificant inflammatory response. Lens substance in vitro, particularly after autolysis, prolonged the survival time of gonococci. No clear evidence of mulitiplication was obtained under these conditions.

DISCUSSION

DR. JAMES H. ALLEN, Iowa City: What was the time interval between injection of lens substance in series 5 and the second inoculation of some of the eyes with injury of the lens?

DR. MAURICE J. DRELL, Chicago: Five days, by which time the reaction from the injection of lens substance had cleared completely.

DR. M. J. HOGAN, San Francisco: Do you think lens substance merely exerts a protective effect on the organisms rather than acting as a culture medium?

DR. MAURICE J. DRELL, Chicago: That question bothered us for a long time. Dr. Miller had been working with the gonococcus for many years, and the project originally was undertaken at the request of the Office of Scientific Research and Development in an effort to produce an experimental infection against which the value of the sulfonamide drugs and other therapeutic agents could be assayed. Theoretically, the gonococcus ought to grow in the presence of lens substance. We tried to make it grow but were unable to obtain any clearcut evidence of its growth. We do know that lens substance is an excellent buffer; the suspension in which lens was present varied only slight from a p_H of 7.4 to one of 7.2 over a period of five days, whereas the p_H of gonococcus suspension alone, in saline or in Ringer's solution, became acid, dropping from 7.4 to 6.8. This is probably one of the essential factors. However, the lens also contains a great many of the nutritive elements on which the gonococcus should be able to live and multiply, and we were unable to demonstrate any multiplication.

The survival time of the individual gonococcus was estimated by Morax to be between three and nine days, the period varying with the strain. The survival time of the gonococcus in our study was eight days. Whether there was any multiplication during this period we are unable to say positively.

DR. V. EVERETT KINSEY, Boston: Were culture mediums containing glutathione or other sulfhydrides tried?

DR. MAURICE J. DRELL, Chicago: The culture medium used was casein digest-cystine agar, prepared in the laboratory. It contained 0.065 per cent cystine, which I believe is a sulfhydride.

DR. V. EVERETT KINSEY, Boston: Cystine or cysteine?

DR. MAURICE J. DRELL, Chicago: Cystine. This medium was used for the recovery of the organisms from infected eyes. The lens itself contains cystine, which is one of the reasons we thought that the gonococcus should be able to grow on it.

DR. WALTER B. LANCASTER, Boston: Will the essayists tell us whether injury to the lens or other optical injury occurs if the gonococci are introduced intravenously or somewhere outside the eye?

DR. MAURICE J. DRELL, Chicago: I presume the question refers to work similar to that reported by Dr. Rosenau with streptococci. I cannot recall any such investigations with gonococci with positive results.

Perhaps a word should be added here. The attempt to produce the gonorrheal iritis is nothing new. It has been tried almost since the time that the organism was first described. The organism apparently needs to have its virulence enhanced in some way. The strain used by us was initially enhanced by something like one hundred and thirty-four passages through the mouse peritoneum before it was sufficiently virulent for the purposes of producing this iritis.

Electroencephalography and Ophthalmology. DR. ALSTON CALLAHAN, Jackson, Miss., and DR. FREDERICK C. REDLICH, Boston.

Electroencephalography is the technic of recording the electrical beat of the brain. In 1902 and 1907, Hans Berger, father of modern

electroencephalography, recorded spontaneous rhythmic fluctuations in the electrical potentials from the brain of animals, and in 1930 he was successful in recording evidence of the electrical activity of the human brain. He showed that normally the beat of the brain appears as a mixture of more or less sinusoidal fluctuation in voltage with a frequency of from 1 to 60 waves per second and that the most commonly recorded rhythm in normal adults has a frequency of approximately 10 per second. Berger proved that this electrical rhythm came from the cortex, and he called the record the electroencephalogram.

The electroencephalogram records electrical activity of the brain from the surface of the scalp, just as the electrocardiogram records that of the heart from the thoracic wall. Like the electrocardiogram, the maximum diagnostic and prognostic value of the electroencephalogram is attained when it is combined with other types of clinical and laboratory examinations.

Electroencephalography has become useful in neurologic diagnosis and has found widespread application. Its greatest usefulness lies in the following fields: (1) the diagnosis of convulsive disorders; (2) the diagnosis and prognosis of head injuries, particularly those accompanied with convlusive seizures; (3) the diagnosis and localization of expanding intracranial lesions, such as tumors, subdural hematoma and cerebral abscess; (4) the diagnosis of narcolepsy, of some types of encephalitis and of the sequelae of meningitis, and (5) the diagnosis of diffuse, inflammatory or degenerative conditions of the brain and of some organic psychoses, and eventually, perhaps, in the diagnosis of personality disorders.

Several problems are of primary interest to ophthalmologists: (1) the local electrical discharges following opening and closing of the eyes and ocular movements, (2) the effect of visual stimulation and opening and closing of the eyes on the occipital electroencephalogram, (3) the diagnosis of false (hysterical or malingered) blindness and (4) the localization of cerebral lesions with visual defects.

Electroencephalography has the following applications in ophthalmology:

1. The electroencephalogram is used to record changes in electrical potentials of the eye after ocular movements. These potentials can be observed only when the retina is present, and they are thought to be due to the chorioretinal difference in potential.

2. Observations on the effect of visual stimulation and the opening and closing of the eyes were inconclusive. In a series of 100 patients, a statistical scatter of findings resulted. In a series of 30 patients with normal brain waves, opening and closing the eyes in the dark had an effect on the normal occipital rhythm similar to that of the visual stimulus in the dark. The normal occipital wave in man can be driven by repetitive photic stimulation of the retina. No characteristic effect was discovered in 10 cases of amblyopia.

3. The effect on the normal occipital rhythm of opening the eyes does not differentiate true from malingered or hysterical blindness.

4. The galvanic cutaneous response to visual stimulation can be used to differentiate true from false blindness.

5. The electroencephalogram is an aid in localizing cerebral lesions with visual defects. Superficial lesions, especially tumors, frequently show slow waves.

DISCUSSION

DR. DAVID HARRINGTON, San Francisco: Was there any correlation between the electroencephalographic pattern and the congruity of the visual fields in the anteroposterior localization of cerebral lesions?

DR. ALSTON CALLAHAN, San Francisco: The question refers to the hypothesis that the more posterior the lesion, the more congruent are the field defects; and Dr. Harrington wishes to know whether we found evidence to support or to disprove this theory. We did not make a study of our cases with this relationship in mind. Case reported 7 cases of homonymous hemianopsia in which operation revealed a tumor of the optic tract and there was loss of normal occipital rhythm over the occipital cortex.

Further Observations on Aqueous Veins. DR. K. W. ASCHER, Cincinnati.

In 1941, for the first time by means of the biomicroscope, aqueous humor was seen to stream through conjunctival and episcleral veins of the normal human eye. Vessels containing a clear fluid, sometimes mixed with varying amounts of blood, can be found in at least one third of all quiet human eyes with the use of the corneal microscope and slit lamp illumination. With the aid of a 10 diameter magnifying loupe and good oblique illumination, they are detectable in more than 14 per cent of all eyes not injected. Emerging from the limbal meshwork, from the depth of the scleral tissue adjacent to the limbus or from a scleral emissarium, these clear vessels join conjunctival or subconjunctival veins. In the recipient vessel, they produce either a considerable dilution of its blood content or a characteristic pattern of stratification with two, three or more differently colored layers, which run parallel to one another along the wall of the vessel. The colorless vessels were termed aqueous veins. They are biomicroscopically visible pathways connecting Schlemm's canal and the intrascleral meshwork with conjunctival and subconjunctival veins. Not all quiet human eyes show aqueous veins, owing to the fact that aqueous humor, on leaving the canal of Schlemm, may become rapidly and completely mixed with the blood which is contained in the intrascleral meshwork. If, however, clear fluid can reach the episcleral or conjunctival veins without the previous addition of too many red blood cells, an aqueous vein will become visible. Anatomic differences in the outlets of Schlemm's canal are rather definite, and it seems reasonable to assume that an outlet measuring 50 microns in diameter will be more important for the elimination of intraocular fluid than another outlet having only one-tenth this diameter. It is possible that in some normal human eyes a great number of outlets are constantly eliminating aqueous humor, whereas in other eyes only a few outlets, or even only one, may carry the bulk of fluid. In eyes of the latter type, surgical or traumatic severing of one of these main channels may initiate a disastrous increase of intraocular pressure.

The possible role of the aqueous veins in the etiology and classification of glaucoma was discussed. Observations on glaucomatous eyes led to the working hypothesis that a transient or permanent narrowing of the outlets of Schlemm's canal may be connected with the presence,

or even may be responsible for the development, of increased intraocular pressure in certain eyes. Clinical observations and reflection suggest the significance of aqueous veins in the mechanism of decompensated glaucoma.

Many ophthalmologists have had difficulty in recognizing the aqueous veins, whereas others have confirmed their occurrence and significance. Photographs of recipient vessels have corroborated the presence of highly diluted blood in these vessels, as well as the influence of drugs on the elimination of intraocular fluid through the aqueuos veins.

Protracted observation of the veins surrounding the corneoscleral junction will always reveal that one or more individual channels are continually charged with the elimination of intraocular fluid. Physiologic factors and climatic differences in part concur in their effect and in part exercise opposing influences on aqueous veins. Once located, the particular aqueous vein remains discoverable at its original location after months and years and retains its characteristic qualities. Apparent differences in the incidence of aqueous veins, when searched for with a 10 diameter magnifying loupe at different seasons of the year, are due to differences in the red cell content and to the greater difficulty of recognizing an aqueous vein when there is conjunctival congestion. In eyes blind from tabetic atrophy of the optic nerve, the movement of the fluid streaming in aqueous veins is often slow.

The question whether aqueous veins contain aqueous humor or blood deprived of all, or part, of its red cell has recently been answered by Goldmann. He stated that after intravenous injection of a 10 per cent solution of fluorescein sodium the aqueous veins remained colorless, while the blood running in the recipient vessels, in conjunctival and in subconjunctival veins, showed the greenish yellow hue of the dye. India ink, injected into the anterior chamber of an eye with a uveal sarcoma, appeared in a previously located aqueous vein only, and not in any of the other vessels.

The physiologic and clinical significance of the aqueous veins should be acknowledged. The term "aqueous veins," should be accepted for the biomicroscopically visible part of the pathways, which are charged with elimination of intraocular fluid from the canal of Schlemm via the intrascleral meshwork to the conjunctival, subconjunctival and anterior ciliary veins.

DISCUSSION

SIR WILLIAM STEWART DUKE-ELDER, London, England: I should like to ask Dr. Ascher one question. He started off by eliminating the arterial system entirely. Does he agree with Dr. Friedenwald that there are direct aberrant arterial vessels in the canal of Schlemm?

DR. K. W. ASCHER: I do not dare to answer that question, for I do not have any pertinent experience of my own.

From the papers published on this subject, I believe that it is possible that these vessels described by Friedenwald not only are present but also fulfill the physiologic function described, or aseribed to them, by Friedenwald.